Report on the Deliberation Results

December 11, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Voydeya Tablets 50 mg
Non-proprietary Name	Danicopan (JAN*)
Applicant	Alexion Pharma GK
Date of Application	May 19, 2023

Results of Deliberation

At its meeting held on December 8, 2023, the First 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. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a very limited number of Japanese subjects participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a certain number of patients have been accumulated, in order to identify the characteristics of these patients, to collect safety and efficacy data on the product without delay, and to take the necessary actions to facilitate the proper use of the product.
3. Prior to marketing, the applicant is also required to take necessary actions to ensure that the product will be administered under the supervision of a suitable physician at a suitable medical institution (i.e., both of which should be familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and be fully capable of managing the risks, etc. associated with the product), in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

** Japanese Accepted Name (modified INN)*

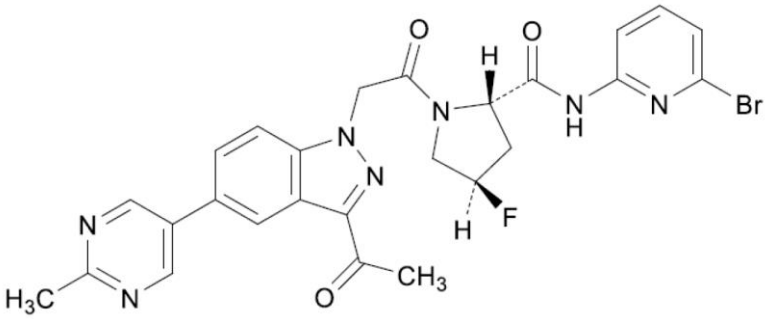
Review Report

November 28, 2023
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Voydeya Tablets 50 mg
Non-proprietary Name	Danicopan
Applicant	Alexion Pharma GK
Date of Application	May 19, 2023
Dosage Form/Strength	Each film-coated tablet contains 50 mg of danicopan.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{26}H_{23}BrFN_7O_3$
Molecular weight: 580.41
Chemical name: (2*S*,4*R*)-1-{[3-acetyl-5-(2-methylpyrimidin-5-yl)-1*H*-indazol-1-yl]acetyl}-*N*-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 556 of 2023 [*R5 yaku*]; PSEHB/PED Notification No. 0222-1 dated February 22, 2023, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of paroxysmal nocturnal hemoglobinuria and 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 at the dosage and administration shown below, under the following conditions.

Indication

Paroxysmal nocturnal hemoglobinuria

Dosage and Administration

The usual adult dosage is danicopan 150 mg administered orally 3 times daily after meals in combination with a complement (C5) inhibitor. In patients with an inadequate response, the dose may be increased to a maximum of 200 mg.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a very limited number of Japanese subjects participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a certain number of patients have been accumulated, in order to identify the characteristics of these patients, to collect safety and efficacy data on the product without delay, and to take the necessary actions to facilitate the proper use of the product.
3. Prior to marketing, the applicant is also required to take necessary actions to ensure that the product will be administered under the supervision of a suitable physician at a suitable medical institution (i.e., both of which should be familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and be fully capable of managing the risks, etc. associated with the product), in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

Attachment

Review Report (1)

November 2, 2023

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

Product Submitted for Approval

Brand Name	Voydeya Tablets 50 mg
Non-proprietary Name	Danicopan
Applicant	Alexion Pharma GK
Date of Application	May 19, 2023
Dosage Form/Strength	Each film-coated tablet contains 50 mg of danicopan.
Proposed Indication	Inhibition of extravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria
Proposed Dosage and Administration	The usual adult dosage is danicopan 150 mg administered orally 3 times daily in combination with ravulizumab or eculizumab. In patients with an inadequate response, the dose may be increased to a maximum of 200 mg 3 times daily according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

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

Paroxysmal nocturnal hemoglobinuria (PNH) is a hematopoietic stem cell disease characterized by chronic intravascular hemolysis as the main symptom. In PNH, acquired mutations in the *phosphatidylinositol glycan class A (PIGA)* gene causes deficiency of terminal complement regulators CD55 and CD59 on the red blood cell surface; this makes the red blood cells susceptible to damage by the membrane attack complex under the complement activation, resulting in chronic intravascular hemolysis (*J Manag Care Spec Pharm*. 2020;26:S14-S20. *Blood*. 2015;126:2459-2465). In Japan, PNH is classified as a designated intractable disease by the Ministry of Health, Labour and Welfare (MHLW Public Notice No. 62, dated January 1, 2015). The current treatment for PNH in Japan consists of the humanized monoclonal antibodies eculizumab (genetical recombination) and ravulizumab (genetical recombination). However, some patients treated with complement C5 inhibitors experience C3-mediated extravascular hemolysis (*Front Immunol*. 2019;10:1157. S*emin Hematol*. 2018;55:130-135), which is considered an issue to be solved in the treatment of PNH. As a drug for the treatment of PNH with an inadequate response to complement C5 inhibitors, the complement C3 inhibitor pegcetacoplan was approved in Japan in March 2023.

Danicopan is a complement factor D inhibitor discovered by Achillion Pharmaceuticals, Inc. (currently, Alexion Pharmaceuticals, Inc.). It inhibits the serine protease activity of complement factor D, which catalyzes the cleavage of complement factor B (the rate-limiting step of the alternative complement pathway), thereby suppressing activation of the alternative complement pathway and deposition of C3 fragments in PNH red blood cells. By this mechanism of action, danicopan is expected to be effective for extravascular hemolysis in some patients with PNH treated with complement C5 inhibitors.

The applicant has recently filed an application for the approval of danicopan, stating that a global phase III study has demonstrated its efficacy and safety in patients with PNH. Danicopan was designated as an orphan drug as of February 22, 2023 (Orphan Drug Designation No. 556 of 2023 [*R5 yaku*]) for the intended indication of "paroxysmal nocturnal hemoglobinuria."

Outside Japan, applications for danicopan have been filed in the US and EU. As of October 2023, danicopan has not yet been approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale yellow powder. The determined general properties include description, solubility, melting point, specific rotation, dissociation constant, partition coefficient, and hygroscopicity. The drug substance is present in at least 7 types of crystalline forms (I-VII). Only the crystalline Form ■ were found to be formed during commercial-scale manufacture, and these crystals were confirmed to be stable at room temperature.

The chemical structure of the drug substance has been elucidated by ultraviolet-visible spectroscopy (UV/VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR), mass spectrometry (MS), and single-crystal X-ray crystallography, X-ray powder diffraction, differential scanning calorimetry, and elemental analysis. The drug substance has 2 asymmetric carbons, and the absolute configuration is *S* for the carbon at position 2 and *R* for that at position 4.

2.1.2 Manufacturing process

The drug substance is synthesized using the following starting materials: [redacted], [redacted], [redacted], [redacted], and [redacted].

The quality control strategy has been designed based on the following investigations (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of proven acceptable ranges (PARs) based on quality risk assessment and design of experiments

Table 1. Summary of control strategy for drug substance

CQA	Control methods
Strength	Manufacturing process, specifications
Description	Manufacturing process, specifications
Identification	Manufacturing process, specifications
Related substances	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
Residual solvents	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
Residue on ignition	Manufacturing process, specifications
Water content	Manufacturing process, specifications

The final synthesis and purification of the drug substance have been defined as critical steps.

2.1.3 Control of the drug substance

The proposed specifications for the drug substance consist of content, description, identification (^{1}H-NMR and high performance liquid chromatography [HPLC]), purity ([redacted], related substances [HPLC], [redacted] [HPLC], [redacted] [HPLC]), residual solvents (gas chromatography [GC]), water content, residue on ignition, [redacted] ([redacted]), and assay (HPLC).

2.1.4 Stability of the drug substance

Table 2 shows the main stability studies performed on the drug substance. Photostability testing showed that the drug substance was photostable.

Table 2. Main stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 pilot-scale batches	25°C ± 2°C	60% ± 5% RH	[redacted] polyethylene bag (double layered) + [redacted] desiccant-containing rigid container	12 months
Accelerated	3 pilot-scale batches	40°C ± 2°C	75% ± 5% RH		6 months

In view of the above, a retest period of [redacted] months was proposed for the drug substance stored in a double-layered [redacted] polyethylene bag placed in a [redacted] desiccant-containing rigid container at [redacted]°C to [redacted]°C according to the ICH Q1E guideline. The long-term testing will be continued for [redacted] months.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is a film-coated tablet. Each tablet contains 50 mg of the drug substance. Since the drug substance is a compound with low water solubility, [redacted] was selected as the drug product. Excipients contained in the drug product are hypromellose acetate succinate, lactose hydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, light anhydrous silicic acid, magnesium stearate, and Opadry [redacted] White [redacted].

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: manufacture of [redacted] of the drug substance, [redacted] mixing, [redacted], [redacted], final mixing, tableting, film coating, and packaging/labeling/storage/testing. In-process control parameters and control values have been established for the following steps: manufacture of [redacted] of the drug substance, tableting, film coating, and packaging/labeling/storage.

The quality control strategy has been designed based on the following investigations (Table 3):

- Identification of CQAs
- Identification of PARs based on quality risk assessment and the design of experiments

Table 3. Summary of control strategy for drug product

CQA	Control methods
Strength	Manufacturing process, specifications
Description (appearance)	Manufacturing process, specifications
Identification	Manufacturing process, specifications
Related substances	Manufacturing process, specifications
Water content	Manufacturing process, specifications
Uniformity of dosage unit	Manufacturing process, specifications
Dissolution	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications

Manufacture of [redacted] of the drug substance and tableting have been defined as critical steps.

2.2.3 Control of the drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (HPLC and UV/VIS), purity (related substances [HPLC]), water content, uniformity of dosage units (strength uniformity test [HPLC]), dissolution (HPLC), [redacted] ([redacted]), and assay (HPLC).

2.2.4 Stability of the drug product

Table 4 shows the main stability studies performed on the drug product. The results demonstrated the stability of the drug product. Photostability testing showed that the drug product was photostable.

Table 4. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 pilot-scale batches	25°C ± 2°C	60% ± 5% RH	Blister pack	12 months
Accelerated	3 pilot-scale batches	40°C ±2°C	75% ± 5% RH		6 months

In view of the above, a shelf life of 24 months was proposed for the drug product stored in a blister pack (polyvinyl chloride film/polychlorotrifluoroethylene/aluminum foil) placed in a paper box at room temperature according to the ICH Q1E guideline. The long-term testing will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of the drug substance and the drug product was controlled in an appropriate manner.

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

Studies on primary pharmacodynamics were conducted to investigate the binding affinity of danicopan to complement factor D, inhibition of activation of the alternative complement pathway, and species specificity. Studies on secondary pharmacodynamics were conducted to investigate the off-target effects of danicopan, effects of danicopan metabolites, and the effect of danicopan on bactericidal activity. Safety pharmacology studies were conducted to investigate effects on the cardiovascular, central nervous, and respiratory systems. Pharmacodynamic drug interaction studies were conducted to investigate the effect of coadministration of danicopan with other complement inhibitors.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity to complement factor D (CTD 4.2.1.1-2 to 4.2.1.1-4; reference data 4.2.1.1-1)

The binding affinity of danicopan to human complement factor D was investigated using surface plasmon resonance. Danicopan bound reversibly to human complement factor D, with an equilibrium dissociation constant (K_D) of 0.54 nmol/L.

In enzyme assays using (a) the natural substrate C3bB[1)] and (b) non-specific minimal thioester substrate, the 50% inhibitory concentration (IC_{50}) of danicopan for the serine protease activity of human complement factor

[1)] An activation product of C3 (i.e., a complex of complement factors B and C3b)

D was (a) 18 nmol/L and (b) 35 nmol/L, respectively. This suggests that danicopan binds directly to human complement factor D to inhibit its serine protease activity.

3.1.1.2 Inhibition of activation of the alternative complement pathway (CTD 4.2.1.1-10 to 4.2.1.1-12)

The inhibitory effect of danicopan on activation of the alternative complement pathway, classical complement pathway, and lectin complement pathway was investigated using human serum spiked with danicopan. The IC_{50} of danicopan for activation of the alternative complement pathway was 27 nmol/L. Danicopan did not directly inhibit activation of the classical complement pathway or the lectin complement pathway.

The inhibitory effect of danicopan on hemolysis was investigated using human PNH-like red blood cells and physiological[2)] human PNH red blood cells, both of which were spiked with danicopan. The IC_{50} of danicopan for hemolysis in human PNH-like red blood cells and physiological human PNH red blood cells was 21 and 37 nmol/L, respectively. The IC_{50} of danicopan for the deposition of C3 fragments mediated by the alternative complement pathway was 96 nmol/L in rabbit red blood cells and 27 nmol/L in human PNH-like red blood cells. Thus, danicopan inhibited hemolysis.

3.1.1.3 Species specificity (CTD 4.2.1.1-7 to 4.2.1.1-9)

The species specificity of the inhibitory effect of danicopan on hemolysis was investigated using cynomolgus monkey, dog, rabbit, rat, and mouse serum spiked with danicopan. The IC_{50} of danicopan for hemolysis in cynomolgus monkey, dog, and rabbit serum was 9.1, 25, and 130 nmol/L, respectively. Danicopan did not inhibit hemolysis in rat or mouse serum up to the highest danicopan concentration studied (10 µmol/L).

3.1.2 *In vivo* studies

3.1.2.1 Inhibition of activation of the alternative complement pathway (CTD 4.2.1.1-13 to 4.2.1.1-19)

In pharmacokinetic (PK)/pharmacodynamic (PD) studies in cynomolgus monkeys, danicopan inhibited activation of the alternative complement pathway and hemolysis by ≥90% and ≥80%, respectively, at plasma danicopan concentrations of ≥150 ng/mL.

In PK/PD studies and toxicity studies [see Section 5.2] in dogs, danicopan inhibited activation of the alternative complement pathway by ≥80% at plasma danicopan concentrations of ≥500 ng/mL. The 50% effective concentration (EC_{50}) of plasma danicopan for hemolysis was 198 ng/mL.

In toxicity studies in rabbits [see Section 5.5], the plasma EC_{50} of danicopan for hemolysis was 1,285 ng/mL.

[2)] Under 72% serum conditions

3.2 Secondary pharmacodynamics

3.2.1 Off-target effects (CTD 4.2.1.2-1, 4.2.1.2-2, and 4.2.1.2-10; reference data 4.2.1.2-3 to 4.2.1.2-9 and 4.2.1.2-11 to 4.2.1.2-18)

The cytotoxicity of danicopan was investigated using human cells (Hep2 cells,[3)] HepG2 cells,[4)] Huh7 cells,[4)] MT4 cells,[5)] peripheral blood mononuclear cells, and primary hepatocytes). The 50% cytotoxic concentration (CC_{50}) of danicopan was 42.4 µmol/L for Hep2 cells, 40.2 µmol/L for HepG2 cells, 38.9 µmol/L for Huh7 cells, >50 µmol/L for MT4 cells, >50 µmol/L for peripheral blood mononuclear cells, and >50 µmol/L for primary hepatocytes. The CC_{50} of danicopan for Hep2 cells, HepG2 cells, and Huh7 cells correspond to 35, 33, and 32 times, respectively, the C_{max} (1.21 µmol/L) following administration of danicopan at the maximum clinical dose (200 mg 3 times daily orally) in patients with PNH.

The mitochondrial toxicity of danicopan was investigated using MT4 and HepG2 cells.[6)] The CC_{50} of danicopan for MT4 cells cultured in a glucose-containing medium and a galactose-containing medium was 66.6 and 58.3 µmol/L, respectively. The CC_{50} of danicopan for HepG2 cells cultured in glucose- and galactose-containing media was >100 µmol/L for both media. The CC_{50} values of danicopan for MT4 and HepG2 cells in each medium were similar, showing that the mitochondrial toxicity of danicopan is low.

The effect of danicopan on cell proliferation was investigated using human red blood cells, bone marrow cells, and megakaryocyte progenitor cells. Danicopan 50 µmol/L did not affect the number of colonies or the size of human red blood cells or bone marrow cells. The IC_{50} of danicopan for the proliferation of megakaryocyte progenitor cells was 49.5 µmol/L, which corresponds to 41 times the C_{max} (1.21 µmol/L) following administration of danicopan at the maximum clinical dose in patients with PNH.

The binding affinity of danicopan to 55 types of receptors, ion channels, and transporters was investigated. Danicopan 10 µmol/L showed binding affinity to human adenosine A_1 receptor, adenosine A_3 receptor, and melatonin receptor subtype 1 (MT_1), and the percent inhibition of ligand binding by danicopan for these receptors was 89%, 77.2%, and 99.2%, respectively. The IC_{50} of danicopan for ligand binding to human adenosine A_1 receptor, adenosine A_3 receptor, and MT_1 was 2.7, 2.7, and 0.0082 µmol/L, respectively, which correspond to 2.2, 2.2, and 0.007 times, respectively, the C_{max} (1.21 µmol/L) following administration of danicopan at the maximum clinical dose in patients with PNH. In safety pharmacology studies [see Section 3.3] and toxicity studies in dogs and rats [see Section 5.2], no central nervous system findings were observed.

The binding affinity of danicopan to 12 types of ion channels related to cardiac function was investigated. Danicopan 5 µmol/L showed binding affinity to human L-type calcium channel (hCavl.2), and the percent inhibition of ligand binding by danicopan was 59.2%. The C_{max} of danicopan 5 µmol/L corresponds to 4.1

3) Cell line derived from human pharyngeal cancer
4) Cell line derived from human hepatic cancer
5) Human T cell-derived cell line
6) Cells in a glucose-containing medium can produce intracellular ATP by glycolytic pathway, showing resistance to mitochondrial toxicity of a test compound. On the other hand, cells in a galactose-containing medium cannot use glycolytic pathway for ATP production, showing a sensitivity to mitochondrial toxicity. Based on this mechanism, mitochondrial toxicity was evaluated by comparing cytotoxicity observed in cells cultured in each medium.

times the C_{max} (1.21 µmol/L) following administration of danicopan at the maximum clinical dose in patients with PNH. Safety pharmacology studies [see Section 3.3] revealed no cardiovascular system findings.

The binding affinity of danicopan to 44 types of receptors related to drug abuse was investigated. Danicopan 10 µmol/L did not show binding affinity to these receptors related to drug abuse.

The effect of danicopan on the hepatobiliary system was investigated. Danicopan inhibited the bile salt export pump in human, dog, and rat hepatocytes, with an IC_{50} of 33.8, 18.9, and 3.4 µmol/L, respectively. Danicopan also inhibited human multidrug resistance protein 3 (MDR3) and multidrug resistance protein 4 (MRP4) transporters, uridine diphosphate glucuronosyltransferase (UGT)1A1, UGT2B7, and farnesyl X nuclear receptor (FXR). The IC_{50} of danicopan for human MDR3 and MRP4 transporters, UGT1A1, and UGT2B7 was 10.9, 3.46, 0.81, and 0.82 µmol/L, respectively. Danicopan 33.3 µmol/L inhibited human FXR by 54%. The IC_{50} of danicopan for the bile salt export pump, human MDR3 and MRP4 transporters, UGT1A1, and UGT2B7 corresponds to 28, 9.0, 2.9, 0.67, and 0.68 times, respectively, the C_{max} (1.21 µmol/L) following administration of danicopan at the maximum clinical dose in patients with PNH. Danicopan 33.3 µmol/L, which was investigated for human FXR, corresponds to 27 times the C_{max} following administration of danicopan at the maximum clinical dose in patients with PNH. Plasma concentrations of danicopan in humans receiving the clinical dose may exceed the IC_{50} of danicopan for UGT1A1 and UGT2B7, but the percentage of unbound danicopan in human plasma is 5.7% to 8.7%; therefore the safety margin of danicopan for UGT1A1 and UGT2B7 is considered to be greater than 0.67 and 0.68 times, respectively. In a clinical pharmacology study of danicopan in healthy adults [see Section 6.2.9], no effect on UGT activity was observed.

In view of the above, the applicant explained that off-target effects of danicopan were unlikely to affect the efficacy and safety of danicopan in clinical use.

3.2.2 Effects of danicopan metabolites (CTD 4.2.1.2-19 to 4.2.1.2-20)

Effects of the major metabolites of danicopan (M173,[7)] M426,[7)], M582,[8)] and M428[9)]) were investigated. The IC_{50} of M426, M582, and M428 for activation of the alternative complement pathway was >1 µmol/L, which was higher than the IC_{50} (27 nmol/L) of danicopan. The CC_{50} of M582 and M428 for Huh7 cells was 88 µmol/L and >200 µmol/L, respectively. The CC_{50} of M582 and M428 for MT4 cells was >100 µmol/L. The CC_{50} of M173, M426, M582, and M428 for HepG2 cells cultured in a glucose- or galactose-containing medium was >100 µmol/L, suggesting that M173, M426, M582, and M428 are unlikely to have cytotoxicity or mitochondrial toxicity.

3.2.3 Effect on bactericidal activity (CTD 4.2.1.2-21 to 4.2.1.2-23)

The effect of danicopan on (a) bactericidal activity of human serum spiked with *Escherichia coli* and (b) opsonophagocytosis by human monocytes and granulocytes spiked with *Escherichia coli* was investigated.

7) Degradation product of amide hydrolysis
8) Carbonyl reduction product, S-form
9) Product of amide hydrolysis and carbonyl reduction

Danicopan did not inhibit the bactericidal activity of human serum or opsonophagocytosis by human monocytes and granulocytes up to the highest concentration studied (31.6 or 10 μmol/L).

The effect of danicopan, compstatin,[10)] and eculizumab on the bactericidal activity of human serum that had been vaccinated with a meningococcal vaccine[11)] and then spiked with an encapsulated meningococcal strain, was investigated. Danicopan did not inhibit the bactericidal activity of human serum that had been vaccinated with a meningococcal vaccine up to the highest concentration studied (1 μmol/L). Compstatin 10 mmol/L[12)] and eculizumab 50 μg/mL[13)] inhibited the bactericidal activity of human serum that had been vaccinated with a meningococcal vaccine.

3.3 Safety pharmacology

Table 5 shows a summary of safety pharmacology studies.

Table 5. Summary of safety pharmacology studies

Organ system evaluated	Test system	Evaluation items/methods, etc.	Danicopan dose	Administration method	Findings	Attached data CTD
Cardiovascular system	HEK293 cells[a)] (3 specimens/group)	hERG current	1, 3, 5, and 10 μmol/L	*In vitro*	10 μmol/L: 29.9% inhibition	4.2.1.3-1
	Dogs (4 males/group)	ECG, systolic and diastolic blood pressure, mean arterial blood pressure, and heart rate	50, 250, and 500 mg/kg	Single dose p.o.	No effect	4.2.1.3-4
Central nervous system	Dogs (4/sex/group)	Behavioral change, postural reaction, and spinal and cranial nerve functions	100, 500, and 1,000 mg/kg	Repeated dose p.o.	No effect	4.2.1.3-5
Respiratory system	Dogs (4/sex/group)	Tidal volume, respiration rate, and minute volume	100, 500, and 1,000 mg/kg	Repeated dose p.o.	No effect	4.2.1.3-5

a) Kidney cells derived from human fetuses

3.4 Pharmacodynamic drug interactions

3.4.1 Effect of coadministration with other complement inhibitors (CTD 4.2.1.4-1 to 4.2.1.4-2)

Rabbit red blood cells were spiked with danicopan and a complement inhibitor (FUT-175,[14)] compstatin, or anti-C5 antibody) to investigate the effects of coadministration of danicopan with another complement inhibitor on activation of the alternative complement pathway and hemolysis.[15)] Coadministration of danicopan with any of these complement inhibitors enhanced the inhibition of activation of the alternative complement pathway and hemolysis.

10) A complement C3 inhibitor

11) A vaccine against meningococcal serogroups A, C, Y, and W and a vaccine against meningococcal serogroup B were both administered to human serum 3 times in total (booster doses were administered 1 and 2 months after the first dose), and serum was collected after the third dose.

12) 40 times the compstatin concentration 250 μmol/L at which hemolysis was inhibited by 90%

13) Required trough concentration of eculizumab (genetical recombination) (*Haematologica*. 2019;104:340-4)

14) Proteolytic enzyme inhibitor

15) The following 2 methods were used for the investigation: [1] Cubic volume was calculated by the 3-dimensional surface plotting proposed by Prichard and Shipman (*Antiviral Res.* 1990;14:181-205). Based on the calculated value, the effects were classified into strong antagonistic interactions, moderate antagonistic interactions, slight antagonistic interactions, additive interactions, slight synergistic interactions, moderate synergistic interactions, or strong synergistic interactions; [2] The weighted mean of combination index (CI) was calculated by the median effect plotting proposed by Chou and Talalay (*Trends Pharmacol Sci*. 1983;4:450-454). Based on the calculated value, the effects were classified into strong antagonistic interactions, antagonistic interactions, moderate antagonistic interactions, slight antagonistic interactions, additive interactions, slight synergistic interactions, moderate synergistic interactions, synergistic interactions, or strong synergistic interactions.

The effect of coadministration of danicopan with compstatin or eculizumab on hemolysis was investigated using human PNH red blood cells spiked with danicopan and compstatin or eculizumab.[15)] Coadministration of danicopan with compstatin or eculizumab enhanced the inhibition of activation of the alternative complement pathway and hemolysis.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological Action

The applicant's explanation about the pharmacological action of danicopan:

PNH red blood cells lack complement regulators CD55 and CD59. Once complement is activated by infection or other causes, complement components C5a and C5b-9 are released due to chronic and uncontrollable cleavage of complement C5, leading to destruction of PNH blood cells and resultant intravascular hemolysis. While complement C5 inhibitors inhibit hemolysis in PNH by inhibiting the cleavage of complement C5 to prevent C5b-9 formation, complement C3 may be accumulated on the membrane of some PNH red blood cells. The C3 accumulation may cause opsonization of complement C3 fragments, resulting in extravascular hemolysis (*Front Immunol*. 2019;10:1157. *J Blood Med*. 2022;13:425-437).

Danicopan inhibits the serine protease activity of complement factor D, which catalyzes the cleavage of complement factor B (the rate-limiting step of the alternative complement pathway), thereby suppressing activation of the alternative complement pathway and deposition of C3 fragments in PNH red blood cells. By this mechanism of action, danicopan is considered to suppress intravascular and extravascular hemolysis in PNH.

Since danicopan inhibited the serine protease activity of complement factor D and activation of the alternative complement pathway in studies on primary pharmacodynamics, it is expected to be effective for PNH.

PMDA's view:

The applicant's explanation is reasonable in view of the results of studies on primary pharmacodynamics submitted. Danicopan is thus expected to be effective for PNH. On the basis of the safety pharmacology study results submitted, danicopan in clinical use is unlikely to affect the cardiovascular, central nervous, or respiratory system.

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

The PK of danicopan was investigated in rats, rabbits, dogs, and monkeys that received danicopan or [^{14}C]-labeled danicopan. Plasma concentrations of danicopan were measured using liquid chromatography-tandem mass spectrometry (LC/MS/MS), with the quantitation limit of 1, 2.44, 9.77, or 10 ng/mL. The radioactivity of [^{14}C]-labeled danicopan was measured using liquid scintillation counter detection or quantitative whole-body autoradiography.

4.1 Absorption

4.1.1 Single-dose studies

4.1.1.1 Single-dose study of danicopan in rats (CTD 4.2.2.2-4)

Table 6 shows PK parameters in male rats that received a single intravenous or oral dose of danicopan.

Table 6. Plasma PK parameters of danicopan following a single dose of danicopan in rats

Route of administration	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)	Bioavailability [b] (%)
i.v.	2	-	-	1,480 ± 144	0.8 ± 0.2	-
p.o.	5	405 ± 334	4.0 (0.5, 4.0)	1,430 ± 370	1.6 ± 0.2	38.7 ± 10.0

Mean ± standard deviation for 3 rats; -, not calculated.
a) Median (minimum, maximum)
b) ($AUC_{0\text{-}inf}$ of danicopan following an oral dose/orally administered dose)/($AUC_{0\text{-}inf}$ of danicopan following an intravenous dose/intravenously administered dose) × 100

4.1.1.2 Single-dose study of danicopan in dogs (CTD 4.2.2.2-1)

Table 7 shows PK parameters in male dogs that received intravenous infusion over 10 minutes or a single oral dose of danicopan.

Table 7. Plasma PK parameters of danicopan following a single dose of danicopan in dogs

Route of administration	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)	Bioavailability [b] (%)
i.v.	10	9,190 ± 646	0.2 (0.2, 0.2)	9,670 ± 1,620	1.5 ± 0.2	-
p.o.	20	642 ± 320	1.0 (1.0, 4.0)	3,050 ± 3,010	2.0 ± 0.1	15.8 ± 15.6

Mean ± standard deviation for 3 dogs; -, not calculated.
a) Median (minimum, maximum)
b) ($AUC_{0\text{-}inf}$ of danicopan following an oral dose/orally administered dose)/($AUC_{0\text{-}inf}$ of danicopan following an intravenous dose/intravenously administered dose) × 100

4.1.1.3 Single-dose study of danicopan in monkeys (CTD 4.2.2.2-3)

Table 8 shows PK parameters in male monkeys that received intravenous infusion over 10 minutes or a single oral dose of danicopan.

Table 8. Plasma PK parameters of danicopan following a single dose of danicopan in monkeys

Route of administration	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)	Bioavailability [b] (%)
i.v.	10	11,700 ± 2,710	0.2 (0.1, 0.3)	5,470 ± 1,250	1.2 ± 0.7	-
p.o.	50	1,740 ± 291	2.0 (1.0, 2.0)	7,280 ± 1,810	3.4 ± 0.2	26.6 ± 6.6

Mean ± standard deviation for 3 monkeys; -, not calculated.
a) Median (minimum, maximum)
b) ($AUC_{0\text{-}inf}$ of danicopan following an oral dose/orally administered dose)/($AUC_{0\text{-}inf}$ of danicopan following an intravenous dose/intravenously administered dose) × 100

4.1.2 Repeated-dose studies

4.1.2.1 Repeated-dose study of danicopan in rats (CTD 4.2.3.2-3)

Toxicokinetics was investigated in male and female rats that received repeated oral doses of danicopan twice daily for 28 days. Table 9 shows the plasma PK parameters of danicopan. The C_{max} and $AUC_{0\text{-}24h}$ of danicopan tended to be higher in females than in males and increased in a less than dose-proportional manner over the dose range studied. The applicant explained that this trend and increase are attributable to the absorption of

danicopan in the digestive tract, which becomes saturated with increasing dose. C_{max} and AUC_{0-24h} tended to be lower on Day 28 than on Day 1. The applicant explained the reason for this trend as follows:

Cytochrome P450 (CYP) enzymes were induced following repeated doses of danicopan in this study, and the C_{max} and AUC_{0-24h} in rats may have decreased due to CYP induction following repeated doses; however, since contribution of CYP to danicopan elimination in humans is small, unlike that in rats [see Section 6.1.1.3], the decreased exposure following repeated doses in rats is considered irrelevant to humans.

Table 9. Plasma PK parameters of danicopan following repeated oral doses of danicopan in rats

Dose (mg/kg/day)	Sex	Measurement time point (Day)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
200	Male	1	7,910	116,000
		28	10,300	97,200
	Female	1	14,600	224,000
		28	19,500	160,000
500	Male	1	17,900	268,000
		28	16,200	144,000
	Female	1	20,500	266,000
		28	21,900	188,000
1,000	Male	1	20,200	312,000
		28	16,900	183,000
	Female	1	26,200	428,000
		28	22,400	273,000

Calculated from the mean at each measurement time point (3 rats/time point).

4.1.2.2 Repeated-dose study of danicopan in dogs (CTD 4.2.3.2-9)

Toxicokinetics was investigated in male and female dogs that received repeated oral doses of danicopan twice daily for 90 days. Table 10 shows the plasma PK parameters of danicopan. The C_{max} and AUC_{0-24h} of danicopan did not clearly differ between the sexes. C_{max} and AUC_{0-24h} increased dose-dependently over the dose range studied.

Table 10. Plasma PK parameters of danicopan following repeated oral doses of danicopan in dogs

Dose (mg/kg/day)	Sex	Measurement time point (Day)	No. of dogs	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
150	Male	1	4	9,700 ± 2,580	58,800 ± 5,330
		90	3	12,600 ± 4,710	70,900 ± 16,800
	Female	1	4	11,800 ± 1,400	73,200 ± 8,260
		90	4	12,700 ± 3,550	81,200 ± 8,200
250	Male	1	4	11,000 ± 1,820	98,400 ± 19,300
		90	4	14,300 ± 3,050	102,000 ± 25,200
	Female	1	4	14,600 ± 3,350	97,500 ± 19,500
		90	3	13,700 ± 3,130	100,000 ± 20,400

Mean ± standard deviation

4.2 Distribution

4.2.1 Tissue distribution in rats (CTD 4.2.2.3-3)

A single oral dose of [^{14}C]-labeled danicopan 20 mg/kg was administered to male albino rats to investigate radioactivity in each tissue[16)] at 1, 24, and 168 hours post-dose. Radioactivity in all tissues peaked by 1 hour-

[16)] Fat (brown and white), adrenal gland (cortex and medulla), bile, blood, bone, bone marrow, brain (cerebrum, cerebellum, and medulla), cecum, epididymis, esophagus, eye (uvea and lens), Harderian gland, heart, kidney (cortex and medulla), large intestine, liver, lung, lymph node, mammary gland, pancreas, pituitary gland, prostate gland, salivary gland, seminal gland, muscle, non-pigmented skin, pigmented skin (pigmented rats only),

pose dose and then decreased over time. Radioactivity in almost all tissues was higher than that in blood, and was particularly high in the bile, liver, and adrenal cortex.

A single oral dose of [^{14}C]-labeled danicopan 20 mg/kg was administered to male pigmented rats to investigate radioactivity in each tissue[16)] at 1, 2, 4, 8, 24, 72, 168, 336, 504, and 672 hours post-dose. Radioactivity in the uvea at 1 hour post-dose was 4.6 times the radioactivity in blood, and was higher than that in albino rats (radioactivity in the uvea at 1 hour post-dose was 0.6 times that in blood). Radioactivity was detected in the uvea and pigmented skin up to 672 hours post-dose. These findings suggested that danicopan bound to melanin. However, the applicant explained that the binding of danicopan to melanin-containing tissues is unlikely to cause any safety concerns, for the following reasons:

- In a phototoxicity study in pigmented rats that received repeated doses of danicopan twice daily for 3 days, no changes suggestive of phototoxicity of danicopan were observed in the eyes or skin [see Section 5.6.1].
- In a global phase III study (Study ALXN2040-PNH-301), the median duration (minimum, maximum) of treatment with danicopan in 84 treated subjects was 427.5 (44.0, 769.0) days, and eye- or skin-related adverse events[17)] that occurred in ≥2 subjects were eczema in 3 of 84 subjects (3.6%), and erythema, acne, and pruritus in 2 of 84 subjects (2.4%) each. The severity of all of these events was Grade 1 or 2. Eye- or skin-related adverse drug reactions (chalazion, erythema, acne, pruritus, and alopecia) were observed only in 1 of 84 subjects each.

4.2.2 Protein binding (CTD 4.2.2.3-1)

The protein binding of [^{14}C]-labeled danicopan (0.1-40 μmol/L) was investigated using mouse, rat, rabbit, dog, and monkey plasma. The protein binding rate was 92.6% to 93.6% (mouse), 87.0% to 88.5% (rat), 88.4% to 91.4% (rabbit), 78.9% to 89.4% (dog), and 94.3% to 96.5% (monkey).

4.2.3 Distribution in blood cells (CTD 4.2.2.3-2)

The distribution of [^{14}C]-labeled danicopan (0.05-10 μmol/L) in blood cells was investigated using rat, dog, and monkey plasma. The blood-to-plasma concentration ratio was 0.79 to 0.84 (rat), 0.68 to 0.94 (dog), and 0.67 to 0.78 (monkey).

4.2.4 Placental transfer in rabbits (CTD 4.2.2.3-5)

Maternal and fetal plasma concentrations of danicopan were measured in pregnant rabbits that received repeated oral doses of danicopan 50 or 250 mg/kg once daily from Gestation Days 12 to 19. The fetal-to-maternal plasma concentration ratio on Gestation Day 19 was 0.025 and 0.023 at 50 and 250 mg/kg, respectively. Thus, danicopan was detected in fetal plasma, showing that danicopan is transferred to fetuses through the placenta in rabbits.

small intestine, stomach, spleen, spinal cord, testis, thymus gland, thyroid gland, and bladder

17) Events classified under MedDRA SOCs “Eye disorders” or “Skin and subcutaneous tissue disorders”

4.3 Metabolism

4.3.1 Investigation of metabolites *in vitro* (CTD 4.2.2.4-2 and 4.2.2.4-8)

Metabolites of danicopan were investigated using mouse, rat, rabbit, dog, and monkey hepatocytes spiked with danicopan (20 μmol/L). Table 11 shows the percentage of each metabolite among all metabolites. The results suggested that the major metabolic pathway is mono-oxidation in mice, amide hydrolysis in rats, rabbits, and dogs, and the combination of amide hydrolysis and carbonyl reduction in monkeys.

Table 11. Percentage of each metabolite among all metabolites (%)

Metabolite	Metabolic pathway	Mice	Rats	Rabbits	Dogs	Monkeys
M426	Amide hydrolysis	7.64	58.6	86.2	84.8	14.2
M428	Amide hydrolysis and carbonyl reduction	-	-	-	-	71.6
M442	Amide hydrolysis and mono-oxidation	22.3	-	1.68	-	-
M582	Carbonyl reduction	-	-	-	-	12.5
M596[a)]	Mono-oxidation	70.1	41.4	9.55	15.2	1.61
M612	Dioxidation	-	-	2.59	-	-

-, not applicable.
a) Total of mono-oxidized forms of any functional group

4.3.2 Percentage of unchanged danicopan and metabolites in plasma, urine, feces, and bile (CTD 4.2.2.4-4 and 4.2.2.4-5)

The percentage of unchanged danicopan and its metabolites in plasma, bile,[18)] urine, and feces was investigated in male and female rats that received a single oral dose of [^{14}C]-labeled danicopan 20 mg/kg. The percentage of unchanged danicopan to the total plasma radioactivity at each time point from 0.25 to 8 hours post-dose was 70.6% to 96.4% (males) and 75.7% to 84.2% (females). M426 was identified as a major plasma metabolite, which accounted for 1.2% to 17.8% (males) and 9.2% to 13.4% (females) of the total plasma radioactivity. In urine, 12.0% (males) and 17.5% (females) of the total administered radioactivity were detected up to 168 hours post-dose. The main analytes detected were M426 (78.4% of the total urinary radioactivity), M596c[19)] (12.8% of the total urinary radioactivity), and unchanged danicopan (3.4% of the total urinary radioactivity) in males, and M426 (81.8% of the total urinary radioactivity) and unchanged danicopan (4.1% of the total urinary radioactivity) in females. In feces, 59.4% (males) and 60.4% (females) of the total administered radioactivity were detected up to 168 hours post-dose. The main analytes detected were M596c (34.4% of the total fecal radioactivity), unchanged danicopan (20.1% of the total fecal radioactivity), and M426 (17.8% of the total fecal radioactivity) in males, and M426 (40.8% of the total fecal radioactivity) and unchanged danicopan (32.0% of the total fecal radioactivity) in females. In bile, 58.6% of the total administered radioactivity was detected up to 48 hours post-dose. The main analytes detected were M772 (glucuronide conjugate of mono-oxidized form) (15.9% of the total administered radioactivity) and M426 (13.6% of the total administered radioactivity), and unchanged danicopan accounted for 0.4% of the total administered radioactivity. The ratio of M596c in feces was higher in males than in females, suggesting that there may be sex differences in oxidative metabolism to produce M596c; the applicant provided the following explanation for this finding:

[18)] Evaluated only in males.
[19)] Mono-oxidation product of acetyl pyrazole group

In rats, the expression of some CYP isoforms (CYP2C11, CYP2C13, CYP3A2, etc.) differs between the sexes (*International Journal of Toxicology*. 2001;20:161-163), and the involvement of CYP enzymes whose expression levels differ between sexes in the oxidative metabolism of M596c may have caused sex differences in the PK of M596c. However, since the major metabolic pathway of danicopan in humans is amide hydrolysis [see Section 6.1.1.3], the sex differences in the metabolism of danicopan observed in rats are unlikely to occur in humans.

The percentage of unchanged danicopan and its metabolites in plasma, urine, and feces was investigated in male dogs that received a single oral dose of [^{14}C]-labeled danicopan 10 mg/kg. The percentage of unchanged danicopan to the total plasma radioactivity was 31.8% to 63.8% at each time point from 0.25 to 4 hours post-dose. M426 was identified as a major plasma metabolite, which accounted for 27.2% to 35.5% of the total plasma radioactivity. In urine, 12.3% of the total administered radioactivity was detected up to 168 hours post-dose. The main analytes detected were M426 (58.0% of the total urinary radioactivity) and M442 (a metabolite formed by mono-oxidation and amide hydrolysis) (41.8% of the total urinary radioactivity). In feces, 81.9% of the total administered radioactivity was detected up to 168 hours post-dose. The main analyte detected was M426 (62.3% of the total fecal radioactivity), and unchanged danicopan accounted for 2.5% of the total fecal radioactivity.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion in rats (CTD 4.2.2.5-1)

In male rats that received a single oral dose of [^{14}C]-labeled danicopan 20 mg/kg, the percentage of radioactivity excreted in urine and feces up to 168 hours post-dose was 12.0% and 68.0%, respectively, of the administered dose.

In bile duct-cannulated male rats that received a single oral dose of [^{14}C]-labeled danicopan 20 mg/kg, the percentage of radioactivity excreted in urine, feces, and bile up to 48 hours post-dose was 17.4%, 20.2%, and 58.6%, respectively, of the administered dose.

4.4.2 Urinary and fecal excretion in dogs (CTD 4.2.2.5-2)

In male dogs that received a single oral dose of [^{14}C]-labeled danicopan 10 mg/kg, the percentage of radioactivity excreted in urine and feces up to 168 hours post-dose was 12.3% and 81.9%, respectively, of the administered dose.

In male dogs that received a single intravenous dose of [^{14}C]-labeled danicopan 5 mg/kg, the percentage of radioactivity excreted in urine and feces up to 168 hours post-dose was 15.3% and 73.2%, respectively, of the administered dose.

4.4.3 Excretion in milk (CTD 4.2.2.3-5)

The concentration of danicopan in milk was measured in female rabbits that received repeated oral doses of danicopan 50 or 250 mg/kg once daily from Postpartum Days 4 to 10. The ratio of “danicopan concentration

in milk on Postpartum Day 10" to "danicopan concentration in maternal plasma on Postpartum Day 9" was 5.47 and 3.52 at 50 and 250 mg/kg, respectively, showing that danicopan is transferred to milk.

4.R Outline of the review conducted by PMDA

On the basis of the non-clinical PK study results submitted and the applicant's explanation, PMDA has concluded that the non-clinical PK of danicopan was evaluated in an appropriate manner.

5. Toxicity and Outline of the Review Conducted by PMDA

To evaluate the toxicity of danicopan, the applicant conducted repeated-dose toxicity studies, genotoxicity studies, reproductive and developmental toxicity studies, and other toxicity studies (phototoxicity study of danicopan and genotoxicity study on impurities). The main study results are presented below.

5.1 Single-dose toxicity

No single dose toxicity studies were conducted. Instead, the acute toxicity of danicopan was evaluated based on (a) the results of repeated-dose toxicity studies in rats and dogs and (b) the results after the initial dose in a carcinogenicity study in rasH2 mice (Table 12). No deaths or signs of acute toxicity were observed, and the approximate lethal dose of danicopan following oral administration was considered to be >1,000 mg/kg in all animal species.

Table 12. Summary of single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg/day)	Main findings	Approximate lethal dose (mg/kg)	Attached data CTD
Male and female rats (Wistar)	p.o.	0,[a] 250, 500, 1,000	None	>1,000	4.2.3.2.3
Male and female dogs (beagle)	p.o.	0,[b] 200, 500, 1,000	None	>1,000	4.2.3.2.5
Male and female rasH2 mice	p.o.	0,[c] 100, 500, 1,000	None	>1,000	4.2.3.4.2.1

a) PEG400:Kolliphor HS 15 (90:10)
b) PEG400:Kolliphor RH40: propylene glycol (84:10.5:5.5)
c) 0.5%HPMC, 0.1% Tween80

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies in rats (1, 3, and 6 months) and repeated oral dose toxicity studies in dogs (14 days, 3 months, and 9 months) were conducted (Table 13). The main target organs were the liver and thyroid gland.

The blood exposure to danicopan at the no observed adverse effect level (NOAEL) following repeated-dose administration for 6 months in rats and 9 months in dogs (1,000 mg/kg/day in rats and 75 mg/kg/day in dogs), was approximately 26 and 5 times, respectively, the estimated exposure at the maximum clinical dose (600 mg/day).

Table 13. Summary of repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Rats (Wistar)	p.o.	1 month (twice daily) + 14-day recovery period	0,[a)] 200, 500, 1,000	≥200: Decreased total bilirubin ≥500: Decreased body weight/weight gain/food consumption; increased liver weight; hypertrophy/eosinophilic change of centrilobular hepatocytes 1,000: Increased thyroid weight; hypertrophy of thyroid follicular cells Reversibility: Reversible	1,000	4.2.3.2.3-1
Rats (Wistar)	p.o.	3 months (twice daily) + 1-month recovery period	0,[a)] 200, 500, 1,000	≥200: Increased liver weight; hypertrophy of centrilobular hepatocytes; hypertrophy of thyroid follicular cells (females); basophilic foci of altered hepatocytes ≥500: Salivation; decreased thyroxin (T4) (males) 1,000: Decreased T4 (females); increased THS (males); thyroid follicular cell adenoma (females)	1,000	4.2.3.2.4
Rats (Wistar)	p.o.	6 months (twice daily)	0,[a)] 200, 500, 1,000	≥200: Salivation; increased body weight/weight gain; increased liver weight (females); hypertrophy of centrilobular hepatocytes; intracytoplasmic granules in hepatocytes and Kupffer cells (females); basophilic foci of altered hepatocytes (females); hypertrophy of thyroid follicular cells ≥500: Dark discoloration of the liver (females); thyroid follicular cell adenoma 500: Hepatic single cell necrosis (females) 1,000: Increased liver weight (males); increased thyroid weight	1,000	4.2.3.2.5
Dogs (beagle)	p.o.	14 days (twice daily) + 14-day recovery period	0,[b)] 100, 500, 1,000	≥500: Vomiting; decreased body weight; increased total bilirubin/serum creatinine 1,000: Decreased red blood cell count/hemoglobin/hematocrit; increased AST/ALT/ALP/GGT/urinary bilirubin; cholestasis (females)	1,000	4.2.3.2.7
Dogs (beagle)	p.o.	3 months (twice daily) + 1-month recovery period	0,[b)] 100, 250, 500, 1,000	Dead animals: 1,000 (1 of 6 males, 1 of 6 females)[c)] ≥100: Hypertrophy/hyperplasia of the bile duct ≥250: Decreased body weight/food consumption; jaundice; increased ALT/AST/ALP/GGT/total bilirubin; increased serum creatinine/globulin; bile pigment deposition in biliary canaliculus/bile pigmentation in the bile canaliculi and hepatocytes ≥500: Dehydration; decreased red blood cell count/hemoglobin/hematocrit 1,000: Increased reticulocytes (females) Reversibility: Reversible	100	4.2.3.2.8
Dogs (beagle)	p.o.	3 months (twice daily)	0,[b)] 150, 250	Dead animals: 250 (1 of 4 females), 150 (1 of 4 males)[d)] 150: Vomiting; decreased weight gain/food consumption; increased AST/ALT/ALP/GGT; hypertrophy/hyperplasia of the bile duct; bile pigment deposition in Kupffer cells (females) 250: Bile pigment deposition in Kupffer cells (males); increased hematopoietic cell density in the bone marrow	150	4.2.3.2.9

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Dogs (beagle)	p.o.	9 months (twice daily) + 3-month recovery period	0,[b] 35, 75, 150	Dead animals: 150 (3 of 4 males, 1 of 4 females), 75 (1 of 4 males)[e] ≥75: Decreased lymphocytes; decreased total white blood cell count; decreased red blood cell count/hemoglobin/hematocrit; increased serum creatinine 150: Decreased weight gain (females); increased AST/ALT/ALP/GGT; hypertrophy/hyperplasia of the bile duct; bile pigment deposition in Kupffer cells/hepatocytes (females) Reversibility: Reversible	75	4.2.3.2.10

a) PEG400:Kolliphor HS 15 (90:10)
b) PEG400:Kolliphor RH40: propylene glycol (84:10.5:5.5)
c) One female and 1 male receiving 1,000 mg/kg/day were euthanized due to intolerability at Week 3.
d) One female receiving 250 mg/kg/day was euthanized due to intolerability on Day 61. Death of 1 male receiving 150 mg/kg/day was considered to be due to incorrectly administered danicopan.
e) Three males and 1 female receiving 150 mg/kg/day were euthanized due to intolerability. The cause of death of 1 male receiving 75 mg/kg/day was not identified; however, since no changes related to danicopan were observed in the histopathological examination or laboratory tests, the death was considered to be unrelated to danicopan.

5.3 Genotoxicity

Genotoxicity studies consisted of an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and an *in vivo* rat micronucleus assay (Table 14). The results were negative in all of these assays. Danicopan is therefore considered unlikely to be genotoxic *in vivo*.

Table 14. Summary of genotoxicity studies

Study		Test system	Metabolic activation (duration)	Concentration (µg/plate or µg/mL) or dose (mg/kg/day)	Result	Attached data CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A	S9− S9+	0,[a] 1.58, 5.0, 15.8, 50, 158, 500, 1,581, 5,000	Negative	4.2.3.3.1.1
	Chromosomal aberration assay in mammalian cells	TK6 cells (human lymphoblast cells)	S9− (4 hours) S9+ (4 hours) S9− (24 hours)	0,[a] 17.4, 30.5, 53.3, 93.3, 163, 285, 417, 500	Negative	4.2.3.3.1.2
In vivo	Rodent micronucleus assay	Male and female rats (Wistar) Bone marrow		0,[b] 200, 500, 1,000 (p.o., twice daily, 28 days)	Negative	4.2.3.3.2.1-1 4.2.3.3.2.1-2

a) DMSO
b) PEG400:Kolliphor HS 15 (90:10)

5.4 Carcinogenicity

A 104-week repeated oral dose carcinogenicity study in rats and a 26-week repeated oral dose carcinogenicity study in Tg-rasH2 mice were conducted. The studies showed that danicopan was non-carcinogenic (Table 15).

Table 15. Summary of carcinogenicity studies

Test system	Route of administration	Administration period	Main lesions	Sex	Dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Attached data CTD
					0[a)]	0[b)]	5	50	500		
				N	50/sex	50/sex	50/sex	50/sex	50/sex		
Male and female rats (Wistar)	p.o.	104 weeks (twice daily)	Neoplastic lesions	None						500	4.2.3.4.1.1
			Non-neoplastic lesions	Papilledema in the kidney; hepatocellular vacuolation; exudate in the nasal cavity Epithelial degeneration, necrosis, or atrophy of the larynx; epithelial degeneration/necrosis/atrophy of the trachea; epithelial degeneration/necrosis of the bronchus; exudate in the airway lumen/alveoli of the lung; macrophage accumulation in the airway lumen/alveoli of the lung							
Male and female mice (Tg-rasH2)	p.o.	26 weeks (once daily)		Sex	Dose (mg/kg/day)					1,500	4.2.3.4.2.1
					0[b)]	0[c)]	250	750	1,500		
				N	25/sex	25/sex	25/sex	25/sex	25/sex		
			Neoplastic and non-neoplastic lesions	None							

a) PEG400:Kolliphor HS 15 (90:10)
b) Physiological saline
c) 0.5% HPMC, 0.1% Tween 80

5.5 Reproductive and developmental toxicity

A study of fertility and early embryonic development to implantation in rabbits, studies of embryo-fetal development in rats and rabbits, and a study of effects on pre- and postnatal development, including maternal function in rabbits were conducted (Table 16).

In studies of embryo-fetal development in rats and rabbits, the exposure to danicopan at the NOAEL (500 mg/kg/day both in rats and rabbits) was approximately 25 and 18 times, respectively, the estimated exposure at the maximum clinical dose (600 mg/day).

Table 16. Summary of reproductive and developmental toxicity studies

Study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Fertility and early embryonic development to implantation	Male and female rabbits (NZW)	p.o.	Male: 28 days before mating to 1 day before necropsy (once daily)	0,[a] 125, 250, 500	≥250: Decreased body weight/weight gain/food consumption/fecal volume	Parental animals (general toxicity): 125 Parental animals (fertility): 250	4.2.3.5.1.1
			Female: 14 days before mating to Gestation Day 7 (once daily)		500: Decreased body weight/weight gain/food consumption/fecal volume	Parental animals (general toxicity): 250 Parental animals (fertility): 250 Early embryonic development: 500	
Embryo-fetal development	Female rats (Wistar)	p.o.	Gestation Days 6 to 17 (twice daily)	0,[b] 200, 500, 1,000	Maternal animals: No particular finding Fetuses: 1,000: Decreased body weight	Parental animals (general toxicity): 1,000 Embryo-fetal development: 500	4.2.3.5.2.1
	Female rabbits (NZW)	p.o.	Gestation Days 7 to 20 (once daily)	0,[a] 200, 500, 1,000	Maternal animals: Death: 1000 (1 of 22 animals) 500 (2 of 22 animals)[c] 1000: Decreased body weight/weight gain/food consumption/fecal volume, abortion[d] Fetuses: 1,000: Decreased body weight (females)	Parental animals (general toxicity): 500 Embryo-fetal development: 500	4.2.3.5.2.3
Pre- and postnatal development, including maternal function	Female rabbits (NZW)	p.o.	Maternal animals: Gestation Day 7 to Lactation Day 41 (once daily)	0,[a] 50, 125, 250	Maternal animals: Death: 125 (1 of 30 animals)[e] F_1 offspring: No particular finding F_2 embryos: No particular finding	Maternal animals (general toxicity): 250 F_1 offspring development: 250 F_2 embryos: 250	4.2.3.5.3.1

a) 0.5%HPMC, 0.1% Tween
b) PEG400:Kolliphor HS 15 (90:10)
c) Two females receiving 500 mg/kg/day were euthanized due to trauma or detection of blood in the cage.
d) Abortion observed in the 1,000 mg/kg/day group was not accompanied by fetal malformation.
e) Death observed in the 125 mg/kg/day group was unrelated to danicopan.

5.6 Other studies

5.6.1 Phototoxicity

A neutral red uptake assay using mouse 3T3 fibroblast cells was conducted, and the result was positive (Table 17). However, skin reactions were not induced under light irradiation following a single oral dose of danicopan in Long Evans rats. Danicopan is therefore unlikely to be phototoxic.

Table 17. Summary of phototoxicity study

Study	Test system	Testing method	Result	Attached data CTD
Phototoxicity	Mouse 3T3 fibroblast cells (Balb/c 3T3)	Danicopan 0,[a)] 0.316, 0.562, 1, 1.78, 3.17, 5.62, 10, and 17.8 µg/mL were added to cells, and UV-A (5 J/cm^2) and UV-B (21.7-23 mJ/cm^2) were irradiated.	Positive	4.2.3.7.7.1-1
	Pigmented rats (Long Evans)	Danicopan 0,[b)] 200, 500, and 1,000 mg/kg/day were administered to rats, and UV-A (10.29 J/cm^2) and UV-B (145 mJ/cm^2) were irradiated.	Negative	4.2.3.7.7.1-2

a) DMSO
b) PEG400:Kolliphor HS 15 (90:10)

5.6.2 Study on purities

A bacterial reverse mutation assay was conducted on Impurity A, which may be contained in the drug substance of danicopan. The result was negative.

5.R Outline of the review conducted by PMDA

On the basis of the study results submitted and the applicant's explanation, PMDA has concluded that there were no particular concerns about the safety of danicopan in clinical use from a toxicological point of view.

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 the global phase III study (Study ALXN2040-PNH-301) as the main evaluation data for the present application. This global phase III study used the tablet containing 50 mg of danicopan (proposed commercial formulation) and that containing 100 mg of danicopan. The equivalence of the two formulations has been confirmed by dissolution testing.

Plasma and urinary concentrations of danicopan were measured using LC/MS/MS, with the quantitation limit of 0.1 or 2.0 ng/mL (plasma) and 0.1 ng/mL (urine). Alternative pathway hemolysis (APH) levels were measured using the hemolysis method.

6.1.1 Studies using human biomaterials

6.1.1.1 Protein binding (CTD 4.2.2.3-1)

The protein binding rates of danicopan in human plasma, human serum albumin solution, and α_1-acidic glycoprotein solution spiked with [^{14}C]-labeled danicopan (0.1-5 µmol/L) were 91.3% to 94.3%, 89.1% to 90.2%, and 62.9% to 76.7%, respectively, suggesting that danicopan binds mainly to albumin in human plasma.

6.1.1.2 Distribution in blood cells (CTD 4.2.2.3-2)

The distribution of [^{14}C]-labeled danicopan (0.05-10 µmol/L) in blood cells was investigated using human blood plasma. The blood-to-plasma concentration ratio was 0.67 to 0.79.

6.1.1.3 Investigation of metabolites *in vitro* (CTD 4.2.2.4-2)

Metabolites of danicopan were investigated using human hepatocytes spiked with danicopan (20 µmol/L). The percentage of each metabolite among all metabolites was 83.7% for M426 (amide-hydrolyzed form), 11.0%

for M428 (a metabolite formed by amide hydrolysis and carbonyl reduction), 4.55% for M582 (carbonyl-reduced form), and 0.83% for M596 (mono-oxidized form). These results suggest that the major metabolic pathway is amide hydrolysis. No human-specific metabolites were identified [see Section 4.3.1]. Since oxidative metabolism accounted for only a small part of the entire metabolism, the applicant explained that the contribution of CYP to danicopan metabolism was small, and that danicopan was unlikely to be subject to drug interactions as a CYP substrate.

6.1.1.4 Inhibition of human hepatic drug-metabolizing enzymes by danicopan (CTD 4.2.2.6-1)

The inhibitory effect of danicopan (0.03-30 μmol/L) on CYP isoforms[20)] (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) was investigated using human hepatic microsomes. Danicopan inhibited CYP1A2 (IC_{50}: >30 μmol/L), CYP2B6 (IC_{50}: 13 μmol/L), CYP2C8 (IC_{50}: 25 μmol/L), CYP2C9 (IC_{50}: 20 μmol/L), CYP2C19 (IC_{50}: 11 μmol/L), CYP2D6 (IC_{50}: 22 μmol/L), and CYP3A (IC_{50}: 14 and 16 μmol/L). The inhibitory effect was not time-dependent for any isoforms.

The inhibitory effect of danicopan (0.03-30 μmol/L) on UGT isoforms[21)] (UGT1A1 and UGT2B7) was investigated using human hepatic microsomes. Danicopan inhibited UGT1A1 and UGT2B7, with an IC_{50} of 0.81 and 0.82 μmol/L, respectively.

The applicant's explanation:
Investigation based on the "Guideline on drug interaction for drug development and appropriate provision of information" (PSEHB/PED Notification No. 0723-4 dated July 23, 2018)" (hereafter referred to as the drug interaction guideline) showed that danicopan may induce drug interactions by inhibiting CYP2B6, CYP2C19, CYP3A, UGT1A1, and UGT2B7.

6.1.1.5 Induction of human hepatic drug-metabolizing enzymes by danicopan (CTD 4.2.2.6-11)

The inductive effect of danicopan (0.1-30 μmol/L) on CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4) was investigated using human hepatocytes. Danicopan did not clearly induce CYP1A2 or CYP2B6. However, the mRNA expression of CYP2C8, CYP2C9, and CYP3A4 generally increased dose-dependently, with a maximum fold induction (fold induction of danicopan 30 μmol/L) of 2.1-fold (29%-60% of the positive control) for CYP2C8, 1.5- to 1.7-fold (26%-42% of the positive control) for CYP2C9, and 3.9- to 16-fold (12%-22% of the positive control) for CYP3A4.

The applicant's explanation:
Investigation based on the drug interaction guideline, etc. showed a low drug interaction potential of danicopan associated with its induction of CYP2C8, CYP2C9, and CYP3A4.

[20)] Substrates evaluated: CYP1A2, phenacetin; CYP2B6, bupropion; CYP2C8, amodiaquine; CYP2C9, diclofenac; CYP2C19, (S)-mephenytoin; CYP2D6, dextromethorphan; CYP3A, midazolam and testosterone.
[21)] Substrates evaluated: UGT1A1, β-estradiol; UGT2B7, zidovudine.

6.1.1.6 Investigation of transporter-mediated transport (CTD 4.2.2.2-11 and 4.2.2.6-3)

Using Caco-2 cell[22)] monolayers, transport of danicopan (5 μmol/L) mediated by breast cancer resistance protein (BCRP) was investigated. The results showed that danicopan was not a substrate of BCRP.

Using Madin-Darby canine kidney (MDCK) cells[23)] engineered to express P-glycoprotein (P-gp), transport of danicopan (5 μmol/L) mediated by P-gp was investigated. The results showed that danicopan was a substrate of P-gp.

Using HEK293 cells engineered to express organic anion transporting polypeptide (OATP)1B1 or OATP1B3, transport of danicopan (1 and 10 μmol/L) was investigated. The results showed that danicopan was not a substrate of OATP1B1 or OATP1B3.

6.1.1.7 Investigation of transporter inhibition (CTD 4.2.2.6-2, 4.2.2.6-4, 4.2.2.6-6, 4.2.2.6-7, and 4.2.2.6-8)

The effect of danicopan (30 μmol/L for OAT1 and 0.1-30 μmol/L for others) on the transport of reference materials[24)] was investigated using MDCK cells engineered to express P-gp and MDCKII cells engineered to express BCRP, OAT1, OAT3, organic cation transporter (OCT)2, OATP1B1, OATP1B3, multidrug and toxic compound extrusion (MATE)1, or MATE2-K. Danicopan inhibited P-gp, BCRP, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K, with an IC_{50} of 3.96, 5.72, >30, 27.4, 10.8, >30, 19.9, and 11.6 μmol/L, respectively. Danicopan did not show a clear inhibitory effect on OAT1.

The applicant's explanation:
Investigation based on the drug interaction guideline showed that danicopan may induce drug interactions by inhibiting P-gp and BCRP.

Using vesicles engineered to express bile salt export pump (BSEP) or multidrug resistance protein 2 (MRP2), the effect of danicopan (0.1-30 μmol/L) on the transport of reference materials[25)] was investigated. Danicopan inhibited BSEP and MRP2 with an IC_{50} of 23.9 and >30 μmol/L, respectively.

Using vesicles engineered to express BSEP, the effect of the metabolites M426, M582, and M428 of danicopan (100 μmol/L for M426 and M428, and 0.3-100 μmol/L for M582) on the transport of the reference material[26)] was investigated. M582 inhibited BSEP with an IC_{50} of 50.4 μmol/L. Other metabolites did not show a clear inhibitory effect.

Using vesicles engineered to express multidrug resistance protein 3 (MRP3) or MRP4 and MDCKII cells engineered to express sodium taurocholate co-transporting polypeptide (NTCP), the effect of danicopan

22) Cell line derived from human colon cancer
23) Cells derived from dog renal tubular epithelium
24) Substrates evaluated: P-gp, [^{3}H]quinidine; BCRP, [^{3}H]prazosin; OAT1 and OAT3, [^{3}H]para-aminohippuric acid; OCT2, MATE1 and MATE2-K, [^{14}C]metformin; OATP1B1, [^{3}H]estradiol-17β-D-glucuronide; OATP1B3, [^{3}H]cholecystokinin octapeptide.
25) Substrates evaluated: BSEP, [^{3}H]taurocholic acid; MRP2, [^{3}H]estradiol-17β-D-glucuronide.
26) Substrate evaluated: BSEP, [^{3}H]taurocholic acid.

(30 μmol/L for NTCP, and 0.3-100 μmol/L for MRP3 and MRP4) on the transport of reference materials[27] was investigated. Danicopan inhibited MRP3 and MRP4 with an IC_{50} of 66.6 and 3.46 μmol/L, respectively. Danicopan did not show a clear inhibitory effect on NTCP.

Using human hepatocytes, the effect of danicopan (0.1-100 μmol/L) on MDR3 activity[28] was investigated. Danicopan inhibited MDR3 with an IC_{50} of 10.9 μmol/L.

6.2 Clinical pharmacology

6.2.1 Phase I single-dose study (food effect and age effect) (CTD 5.3.3.1-6: Study No. ACH471-016 [2020 to 2021])

A randomized, open-label, 2-group 2-period crossover (Part 1) and single-group (Part 2) study was conducted at 1 foreign study site to investigate the effects of food (Part 1) and age (Part 2) on the safety and PK of a single oral dose of danicopan in non-Japanese healthy young adults[29] (Part 1: target sample size, 20 subjects) and non-Japanese healthy elderly subjects[30] (Part 2: target sample size, 12 subjects).

Part 1: Food effect

Danicopan 200 mg was administered as a single oral dose under fasted conditions or at 30 minutes after the start of intake of a high-fat diet.[31] A 7-day washout period was required after each period.

All of 18 subjects who received danicopan were included in the safety analysis population and the PK analysis population.[32]

Table 18 shows plasma PK parameters of danicopan following a single oral dose of danicopan under fasted and fed conditions in non-Japanese healthy young adults. The ratio (fed/fasted) of the geometric means of C_{max} and $AUC_{0\text{-}inf}$ [90% confidence interval (CI)] was 1.93 [1.63, 2.29] and 1.25 [1.17, 1.35], respectively, suggesting that food affects the PK of danicopan.

Table 18. Plasma PK parameters of danicopan following a single oral dose of danicopan under fasted and fed conditions in non-Japanese healthy young adults

Administration condition	N	C_{max} (ng/mL)	t_{max} [a] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
Fasted	17	480 ± 275	2.5 (1.0, 6.0)	2,812 ± 809	8.8 ± 3.4
Fed	17	878 ± 323	3.0 (1.5, 8.0)	3,620 ± 935	7.2 ± 2.4

Mean ± standard deviation
a) Median (minimum, maximum)

As for safety, adverse events were observed in 11.8% (2 of 17) of subjects in both the fasted and fed administration periods, and adverse drug reactions were observed in 5.9% (1 of 17) of subjects in the fed

[27] Substrates evaluated: MRP3 and MRP4, [^{3}H]estradiol-17β-D-glucuronide; NTCP, [^{3}H]taurocholic acid.
[28] Evaluated using MDR3cyte.
[29] Aged ≥18 to ≤55 years
[30] Aged ≥65 years old
[31] Total calories were approximately 900 kcal, with lipids accounting for approximately 55%.
[32] Two subjects (one receiving the study drug under fasted conditions and the other under fed conditions) did not complete the study treatment and discontinued the study.

administration period. There were no adverse events that resulted in death, were serious, or led to treatment discontinuation.

Part 2: Age effect

Danicopan 200 mg was administered as a single oral dose at 30 minutes after the start of intake of a moderate-fat diet.[33)]

All of 7 subjects who received danicopan were included in the PK analysis population and the safety analysis population.

Table 19 shows plasma PK parameters of danicopan following a single oral dose of danicopan under fed conditions in non-Japanese healthy elderly subjects. $AUC_{0\text{-}inf}$ following a single oral dose of danicopan was slightly lower in healthy elderly subjects than in young adults (Table 18). However, the exposure to danicopan was estimated to be higher after intake of a high-fat diet than after intake of a standard diet in a population PK analysis, and age was not considered to be a covariate that would significantly affect the PK parameters of danicopan [see Section 6.2.13]. Therefore, the applicant explained that the difference in $AUC_{0\text{-}inf}$ was attributable to the difference in dietary content.

Table 19. Plasma PK parameters of danicopan following a single oral dose of danicopan under fed conditions in non-Japanese healthy elderly subjects

N	C_{max} (ng/mL)	t_{max} a) (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
7	635 ± 170	4.0 (2.5, 6.0)	3,245 ± 571	8.8 ± 3.9

Mean ± standard deviation
a) Median (minimum, maximum)

As for safety, adverse events were observed in 14.3% (1 of 7) of subjects. There were no adverse drug reactions or adverse events that resulted in death, were serious, or led to treatment discontinuation.

6.2.2 Phase I single-dose study in Japanese healthy adults (CTD 5.3.3.3-3: Study No. ALXN2040-HV-101 [August to September 2020])

A randomized, open-label, 3-group 3-period crossover study was conducted at 1 foreign study site to investigate the PK and safety following a single oral dose of danicopan in Japanese healthy young adults (target sample size, 9 subjects).

A single oral dose of danicopan 200 mg was administered under fasted conditions or at 30 minutes after the start of intake of a high-fat diet,[34)] or a single oral dose of danicopan 400 mg was administered at 30 minutes after the start of intake of a high-fat diet. A 7-day washout period was required after each period.

33) Total calories were approximately 600 kcal, with lipids accounting for approximately 30%.
34) Total calories were approximately 800 to 1,000 kcal, with lipids accounting for ≥50%.

All of 9 subjects who received the study drug were included in the safety analysis population and the PK analysis population.

Table 20 shows plasma PK parameters of danicopan following a single oral dose of danicopan.

Table 20. Plasma PK parameters of danicopan following a single oral dose of danicopan in Japanese healthy adults

Danicopan dose	Administration condition	N	C_{max} (ng/mL)	t_{max} [a)] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
200 mg	Fasted	9	651 ± 412	2.5 (1.0, 6.0)	3,059 ± 1,042	9.0 ± 5.6
	Fed	9	883 ± 348	3.0 (2.0, 8.4)	4,201 ± 849	6.9 ± 2.5
400 mg	Fed	9	1,694 ± 759	4.0 (2.0, 8.1)	8,280 ± 2,215	7.5 ± 2.8

Mean ± standard deviation
a) Median (minimum, maximum)

As for safety, adverse events were observed in 11.1% (1 of 9) of subjects in the danicopan 200 mg fasted administration period, 11.1% (1 of 9) of subjects in the 200 mg fed administration period, and 11.1% (1 of 9) of subjects in the 400 mg fed administration period. Adverse drug reactions were observed in 11.1% (1 of 9) of subjects in the danicopan 400 mg fed administration period. There were no adverse events that resulted in death, were serious, or led to treatment discontinuation.

6.2.3 Phase I multiple-dose study (CTD 5.3.3.1-2: Study No. ACH471-002 [May 2016 to January 2017])

A placebo-controlled, randomized, double-blind study was conducted at 1 foreign study site to investigate the PK and safety following multiple oral doses of danicopan in non-Japanese healthy adults (target sample size, 46 subjects [14 in the placebo group and 32 in the danicopan group]).

Danicopan 200, 500, or 800 mg was administered orally twice daily for 14 days under fasted conditions or danicopan 75 mg was administered orally 3 times daily for 7 days under fasted conditions.

All of 45 subjects who received the study drug were included in the safety analysis population. Of them, 31 subjects who received danicopan were included in the PK analysis population.

Table 21 shows plasma PK parameters of danicopan following multiple oral doses of danicopan. C_{max} and AUC_{tau} on Day 14 generally increased dose-dependently over the dose range studied (200-800 mg). In the dose range up to danicopan 500 mg, the C_{max} and AUC_{tau} of danicopan on Day 1 were similar to those after the end of multiple-dose administration, showing no clear accumulation associated with multiple oral doses.

Table 21. Plasma PK parameters of danicopan following multiple oral doses of danicopan under fasted conditions in non-Japanese healthy adults

Danicopan dose	Measurement time point	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
200 mg twice daily	Day 1	8	944 ± 471	2,340 ± 613	-
	Day 14	8	901 ± 248	2,470 ± 871	7.4 ± 1.3
500 mg twice daily	Day 1	7	1,550 ± 558	4,300 ± 1,370	-
	Day 14	7	1,870 ± 547	5,220 ± 1,290	6.3 ± 0.6
800 mg twice daily	Day 1	8	1,980 ± 523	6,830 ± 1,010	-
	Day 14	8	3,730 ± 1,710	10,500 ± 2,160	7.8 ± 5.2
75 mg 3 times daily	Day 1	8	615 ± 234	1,140 ± 270	-
	Day 7	8	569 ± 233	1,170 ± 378	9.9 ± 2.8

Mean ± standard deviation; -, not calculated.

As for safety, adverse events were observed in 78.6% (11 of 14) of subjects in the placebo group, 75.0% (6 of 8) of subjects in the danicopan 200 mg group, 100.0% (7 of 7) of subjects in the 500 mg group, 87.5% (7 of 8) of subjects in the 800 mg group, and 75.0% (6 of 8) of subjects in the 75 mg group. Adverse drug reactions were observed in 57.1% (8 of 14) of subjects in the placebo group, 25.0% (2 of 8) of subjects in the danicopan 200 mg group, 42.9% (3 of 7) of subjects in the 500 mg group, and 87.5% (7 of 8) of subjects in the 800 mg group. A serious adverse event was observed in 12.5% (1 of 8) of subjects in the danicopan 200 mg group (fracture displacement), but was unrelated to the study drug. There were no adverse events that resulted in death or led to treatment discontinuation.

6.2.4 Phase I study (mass balance study) (CTD 5.3.3.1-3: Study No. ACH471-005 [September to October 2017])

An open-label study was conducted at 1 foreign study site to investigate mass balance, etc. following a single oral dose of [^{14}C]-labeled danicopan in non-Japanese healthy adult men (target sample size, 8 subjects).

[^{14}C]-labeled danicopan 150 mg was administered as a single oral dose under fasted conditions.

All of 8 subjects who received the study drug were included in the PK analysis population.

Table 22 shows the plasma PK parameters of unchanged danicopan. The percentage of $AUC_{0.5\text{-}4h}$ of unchanged danicopan, M426, and M428[35)] to the total plasma radioactivity up to 4 hours post-dose was 22.9%, 52.5%, and 11.0%, respectively, showing that metabolites were mainly detected in plasma.

Table 22. Plasma PK parameters of unchanged danicopan following a single oral dose of [^{14}C]-labeled danicopan under fasted conditions in non-Japanese healthy adults

Danicopan dose	N	C_{max} (ng/mL)	t_{max}[a)] (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
150 mg	8	652 (44.8)	1.1 (0.8, 2.0)	1,730 (24.0)	5.8 (19.4)

Geometric mean (coefficient of variation %)
a) Median (minimum, maximum)

35) Including isomer mixture.

The percentage of radioactivity of [^{14}C]-labeled danicopan excreted in urine and feces up to 216 hours post-dose was 24.8% and 69.2%, respectively, of the administered radioactivity. In urine up to 24 hours post-dose, M426 was mainly detected (14.4% of the total administered radioactivity), with M428[35)] and unchanged danicopan accounting for 6.96% and 0.48%, respectively, of the administered radioactivity. In feces up to 168 hours post-dose,[36)] M426 was mainly detected (32.8% of the total administered radioactivity), with M428[35)] and unchanged danicopan accounting for 10.8% and 3.57%, respectively, of the administered radioactivity.

6.2.5 Phase I study (effect of renal impairment) (CTD 5.3.3.3-1: Study No. ACH471-009 [January to May 2018])

An open-label study was conducted at 4 foreign study sites to investigate the effect of renal impairment on the PK of danicopan in non-Japanese subjects with normal renal function and subjects with severe (non-dialysis) renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2 or CL_{cr} <30 mL/min) (target sample size, 16 subjects [8 in each group]).

Danicopan 200 mg was administered as a single oral dose under fed conditions.

All of 16 subjects who received the study drug were included in the safety analysis population and the PK analysis population.

As for the plasma PK parameters of danicopan, the geometric mean ratios (subjects with severe renal impairment/subjects with normal renal function) of C_{max} and $AUC_{0\text{-}inf}$ [90% CI] were 0.94 [0.74, 1.19] and 1.52 [1.19, 1.94], respectively. The $AUC_{0\text{-}inf}$ increased in subjects with severe renal impairment.

As for safety, adverse events were observed in 37.5% (3 of 8) of subjects with normal renal function, and adverse drug reactions in 25.0% (2 of 8) of subjects with normal renal function. There were no adverse events that resulted in death, were serious, or led to treatment discontinuation.

6.2.6 Phase I study (effect of hepatic impairment) (CTD 5.3.3.3-2: Study No. ACH471-012 [May to September 2018])

An open-label study was conducted at 2 foreign study sites to investigate the effect of hepatic impairment on the PK of danicopan in non-Japanese subjects with normal hepatic function and subjects with moderate hepatic impairment (Child-Pugh Class B) (target sample size, 48 subjects; Part 1, 16 subjects [8 in the normal hepatic function group and 8 in the moderate hepatic impairment group]; Part 2, 32 subjects [16 in the normal hepatic function group, 8 in the mild hepatic impairment group, and 8 in the severe hepatic impairment group][37)]).

Danicopan 200 mg was administered as a single oral dose under fed conditions.

[36)] Mean in subjects with different sampling intervals during 0 to 168 hours

[37)] The results of Part 1 suggested that moderate hepatic impairment was unlikely to have clinically problematic effects on the PK of danicopan. Therefore, Part 2 was not conducted.

All of 16 subjects who received the study drug were included in the safety analysis population and the PK analysis population.

As for the plasma PK parameters of danicopan, the geometric mean ratios (subjects with moderate hepatic impairment/subjects with normal hepatic function) of C_{max} and $AUC_{0\text{-}inf}$ [90% CI] were 0.73 [0.55, 0.95] and 0.92 [0.79, 1.09], respectively.

As for safety, no adverse events were observed.

6.2.7 Foreign Phase II study (CTD 5.3.5.2-2: Study No. ACH471-101 [May 2018 to January 2023])

PK following multiple oral doses of danicopan was investigated in patients with PNH with an inadequate response to eculizumab [see Section 7.1.1 for a study outline and the efficacy and safety results].

The starting dose of danicopan was 100 or 150 mg administered orally 3 times daily. Dose increase to up to 200 mg 3 times daily was allowed.

Table 23 shows plasma PK parameters at Week 12 following multiple oral doses of danicopan.

Table 23. Plasma PK parameters at Week 12 following oral doses of danicopan 3 times daily in non-Japanese patients with PNH

Danicopan dose	N	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{tau} (ng·h/mL)
100 mg	6	402 ± 165	2.8 (1.6, 3.1)	1,610 ± 385
150 mg[b)]	4	410 ± 122	1.6 (1.0, 2.0)	1,890 ± 788
200 mg[c)]	1	699[d)]	2.5[d)]	3,070[d)]

Mean ± standard deviation
a) Median (minimum, maximum)
b) Including 1 subject with dose increase to 150 mg at Week 12.
c) The dose was increased to 200 mg at Week 12.
d) Individual data of 1 subject

6.2.8 Global phase III study (CTD 5.3.5.1-1: Study No. ALXN2040-PNH-301 [[redacted] 20[redacted] to data cut-off of [redacted] 20[redacted]; ongoing as of [redacted] 20[redacted]])

PK and PD following multiple oral doses of danicopan were investigated in patients with PNH with an inadequate response to ravulizumab or eculizumab [see Section 7.2.1 for a study outline and the efficacy and safety results].

The study consisted of 3 parts: a double-blind period of 12 weeks (treatment with placebo or danicopan), a continued danicopan treatment period of 12 weeks (treatment with danicopan), and an extension period of up to 2 years (treatment with danicopan).

Placebo or danicopan 100 or 150 mg was administered orally 3 times daily. Dose increase to 200 mg 3 times daily was allowed at Weeks 4, 12, 18, and 24 [see Section 7.2.1 for the starting dose and detailed method for dose increase].

For PK, Table 24 shows changes in plasma danicopan concentration during the study period. C_{trough} tended to be higher in the Japanese subpopulation than in the entire population and the non-Japanese subpopulation.

Table 24. C_{trough} (ng/mL) of danicopan in patients with PNH

	Treatment group	Dose	Double-blind period		Continued danicopan treatment period	
			Week 4	Week 12	Week 16	Week 24
Entire population	Danicopan	100 mg	-	-	167[a)]	-
		150 mg	240 ± 227(50)	219 ± 180 (36)	279 ± 271 (17)	319 ± 310 (11)
		200 mg	-	316 ± 348 (9)	291 ± 284 (26)	245 ± 273 (27)
	Placebo	150 mg	-	-	214 ± 208 (22)	140 ± 96 (8)
		200 mg	-	-	-	240 ± 211 (12)
Japanese subpopulation	Danicopan	150 mg	350 ± 259 (7)	353 ± 290 (6)	729[b)]	-
		200 mg	-	203[a)]	273 ± 326 (4)	560 ± 466 (5)
	Placebo	150 mg	-	-	561 ± 372 (3)	204[a)]
		200 mg	-	-	-	669[a)]
Non-Japanese subpopulation	Danicopan	100 mg	-	-	167[a)]	-
		150 mg	222 ± 219 (43)	193 ± 142 (30)	219 ± 225 (15)	319 ± 310 (11)
		200 mg	-	330 ± 369 (8)	294 ± 284 (22)	174 ± 147 (22)
	Placebo	150 mg	-	-	159 ± 108 (19)	130 ± 99 (7)
		200 mg	-	-	-	201 ± 171 (11)

Mean ± standard deviation (No. of subjects); -, not applicable.
a) Individual data of 1 subject
b) Mean of 2 subjects

For PD, Table 25 shows changes in APH levels. The mean APH levels after administration of danicopan were <10% at most of the time points in all of the Japanese and non-Japanese subpopulations and the entire population.

Table 25. Mean APH levels (%) in patients with PNH

	Treatment group	Measurement timing	Double-blind period			Continued danicopan treatment period	
			Day 1	Week 4	Week 12	Week 16	Week 24
Entire population	Danicopan	Pre-dose	31.6 ± 28.2 (57)	7.9 ± 12.7 (52)	5.8 ± 5.6 (46)	9.5 ± 16.6 (46)	12.6 ± 20.6 (38)
		Post-dose[a)]	9.9 ± 13.5 (43)	6.1 ± 8.0 (47)	5.6 ± 4.9 (46)	5.4 ± 5.1 (43)	5.0 ± 3.6 (36)
	Placebo	Pre-dose	36.4 ± 25.1 (28)	42.1 ± 30.0 (26)	40.3 ± 20.2 (24)	9.5 ± 11.0 (21)	8.0 ± 7.0 (18)
		Post-dose[a)]	37.4 ± 23.5 (21)	34.7 ± 28.4 (21)	13.2 ± 16.1 (19)[b)]	6.8 ± 7.0 (21)	5.1 ± 4.5 (18)
Japanese subpopulation	Danicopan	Pre-dose	17.1 ± 12.6 (8)	4.0 ± 1.7 (7)	3.7 ± 2.6 (7)	7.0 ± 6.9 (6)	2.7 ± 2.3 (5)
		Post-dose[a)]	3.9 ± 2.5 (7)	5.6 ± 2.3 (7)	3.3 ± 1.3 (7)	4.8 ± 3.9 (6)	3.8 ± 3.5 (5)
	Placebo	Pre-dose	41.2 ± 33.1 (4)	59.4 ± 34.8 (4)	48.1 ± 32.2 (4)	7.7 ± 7.1 (3)	4.4[c)] (2)
		Post-dose[a)]	40.8 ± 36.7 (4)	42.9 ± 26.1 (4)	10.1 ± 14.3 (4)[b)]	4.6 ± 2.8 (3)	2.1[c)] (2)
Non-Japanese subpopulation	Danicopan	Pre-dose	33.9 ± 29.4 (49)	8.5 ± 13.6 (45)	6.2 ± 6.0 (39)	9.9 ± 17.6 (40)	14.1 ± 21.7 (33)
		Post-dose[a)]	11.1 ± 14.5 (36)	6.2 ± 8.6 (40)	6.0 ± 5.1 (39)	5.5 ± 5.3 (37)	5.2 ± 3.7 (31)
	Placebo	Pre-dose	35.6 ± 24.4 (24)	38.9 ± 28.8 (22)	38.8 ± 17.8 (20)	9.8 ± 11.7 (18)	8.5 ± 7.3 (16)
		Post-dose[a)]	36.6 ± 20.9 (17)	32.8 ± 29.3 (17)	14.0 ± 16.9 (15)[b)]	7.1 ± 7.5 (18)	5.5 ± 4.6 (16)

Mean ± standard deviation (No. of subjects)
a) APH level at 2 ± 0.5 hours after danicopan administration
b) Value after study drug (danicopan) administration in the continued treatment period
c) Mean of 2 subjects

6.2.9 Phase I study (drug interactions with midazolam, fexofenadine, and mycophenolate mofetil) (CTD 5.3.3.4-1: Study No. ACH471-010 [April to June 2017])

A study was conducted to investigate the effect of danicopan on the PK of midazolam (substrate of CYP3A), fexofenadine (substrate of P-gp and OATP1B1[38)]), and mycophenolate mofetil (mycophenolic acid [substrate of UGT]) in non-Japanese healthy adults (target sample size, 36 subjects).

Table 26 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of midazolam, fexofenadine, and mycophenolic acid and mycophenolic acid glucuronide coadministered with danicopan to those of these drugs administered without danicopan.

Table 26. Geometric mean ratios (coadministration with danicopan/without danicopan) of plasma PK parameters of midazolam, fexofenadine, and mycophenolic acid and mycophenolic acid glucuronide

Danicopan (p.o.)	Concomitant drug	Analyte	N	C_{max}	$AUC_{0\text{-}inf}$
150 mg 3 times daily	Midazolam[a)]	Midazolam	11	1.22 [1.07, 1.39]	1.23 [1.16, 1.31]
	Fexofenadine[b)]	Fexofenadine	12	1.42 [1.28, 1.59]	1.62 [1.47, 1.79][d)]
	Mycophenolate mofetil[c)]	Mycophenolic acid	11	0.99 [0.72, 1.36]	1.05 [0.95, 1.15][e)]
		Mycophenolic acid glucuronide	11	0.88 [0.72, 1.07]	0.93 [0.90, 0.96]

Geometric mean ratio [90% CI]

a) In Period 1, midazolam 2 mg was administered as a single oral dose on Day 1. In Period 2, danicopan was administered orally 3 times daily after meals on Days 1 to 4, and midazolam 2 mg was coadministered with danicopan on Day 4. The washout period between Periods 1 and 2 was ≥3 days. The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}inf}$ of midazolam in the presence of danicopan" to "C_{max} or $AUC_{0\text{-}inf}$ of midazolam in the absence of danicopan."

b) In Period 1, fexofenadine 180 mg was administered as a single oral dose on Day 1. In Period 2, danicopan was administered orally 3 times daily after meals on Days 1 to 6, and fexofenadine 180 mg was coadministered with danicopan on Day 4. The washout period between Periods 1 and 2 was ≥3 days. The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}inf}$ of fexofenadine in the presence of danicopan" to "C_{max} or $AUC_{0\text{-}inf}$ of fexofenadine in the absence of danicopan."

c) In Period 1, mycophenolate mofetil 1 g was administered as a single oral dose on Day 1. In Period 2, danicopan was administered orally 3 times daily after meals on Days 1 to 6, and mycophenolate mofetil 1 g was coadministered with danicopan on Day 4. The washout period between Periods 1 and 2 was ≥3 days. The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}inf}$ of mycophenolate mofetil in the presence of danicopan" to "C_{max} or $AUC_{0\text{-}inf}$ of mycophenolate mofetil in the absence of danicopan."

d) 11 subjects

e) 10 subjects

6.2.10 Phase I study (drug interactions with ciclosporin, tacrolimus, calcium carbonate, aluminum hydroxide, magnesium hydroxide, simethicone, and omeprazole) (CTD 5.3.3.4-2: Study No. ACH471-014 [July to October 2018])

A study was conducted to investigate the effect of danicopan on the PK of ciclosporin (substrate of CYP3A), tacrolimus (substrate of CYP3A and P-gp), and omeprazole (substrate of CYP2C19), and the effect of ciclosporin (P-gp inhibitor), calcium carbonate, aluminum hydroxide, magnesium hydroxide, simethicone (antacid), and omeprazole on the PK of danicopan in non-Japanese healthy adults (target sample size, 72 subjects).

Table 27 shows the geometric mean ratios of C_{max} and AUC of ciclosporin, tacrolimus, and omeprazole and 5-hydroxy omeprazole coadministered with danicopan to those of these drugs administered without danicopan.

[38)] Besides P-gp and OATP1B1, danicopan inhibited OAT3, OATP1B1, OATP1B3, MATE1, and MATE2-K in *in vitro* studies. Fexofenadine serves as a substrate of these transporters.

Table 27. Geometric mean ratios (coadministration with danicopan/without danicopan) of PK parameters of ciclosporin, tacrolimus, and omeprazole and 5-hydroxy omeprazole

Danicopan (p.o.)	Concomitant drug	Analyte	N	C_{max}	AUC
200 mg 3 times daily	Ciclosporin[a)]	Ciclosporin	14	1.03 [0.95, 1.11]	1.20 [1.14, 1.25]
	Tacrolimus[b)]	Tacrolimus	27	1.13 [1.02, 1.25]	1.49 [1.40, 1.59]
	Omeprazole[c)]	Omeprazole	27	1.24 [0.98, 1.57]	1.17 [0.99, 1.38]
		5-hydroxy omeprazole	27	1.11 [0.93, 1.32]	1.06 [0.95, 1.17]

Geometric mean ratio [90% CI]

a) In Period 1, ciclosporin 300 mg was administered as a single oral dose on Day 1. In Period 2, danicopan was administered orally 3 times daily after meals on Days 1 to 7, and ciclosporin 300 mg was coadministered with danicopan on Day 5. The washout period between Periods 1 and 2 was ≥3 days. The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}inf}$ of ciclosporin in the presence of danicopan" to "C_{max} or $AUC_{0\text{-}inf}$ of ciclosporin in the absence of danicopan."

b) In Period 1, tacrolimus 2 mg was administered as a single oral dose on Day 1. In Period 2, danicopan was administered orally 3 times daily after meals on Days 1 to 10, and tacrolimus 2 mg was coadministered with danicopan on Day 5. The washout period between Periods 1 and 2 was ≥7 days. The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}inf}$ of tacrolimus in the presence of danicopan" to "C_{max} or $AUC_{0\text{-}inf}$ of tacrolimus in the absence of danicopan."

c) In Period 1, omeprazole 40 mg was orally administered once daily on Days 1 to 4. In Period 2, danicopan was administered orally 3 times daily after meals, and omeprazole 40 mg orally once daily after a meal, on Days 5 to 8 (omeprazole 40 mg was coadministered with danicopan on Days 5 to 8). The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}24h}$ of omeprazole in the presence of danicopan" to "C_{max} or $AUC_{0\text{-}24h}$ of omeprazole in the absence of danicopan."

Table 28 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}8h}$ of danicopan coadministered with ciclosporin, calcium carbonate, aluminum hydroxide/magnesium hydroxide/simethicone, or omeprazole to those of danicopan administered without these drugs.

Table 28. Geometric mean ratios (coadministration with a drug[s]/danicopan alone) of plasma PK parameters of danicopan (concomitant drugs: ciclosporin, calcium carbonate, aluminum hydroxide/ magnesium hydroxide/simethicone, or omeprazole)

Danicopan (p.o.)	Concomitant drug(s)	N	C_{max}	$AUC_{0\text{-}8h}$
200 mg 3 times daily	Ciclosporin[a)]	14	1.14 [0.98, 1.34]	1.21 [1.11, 1.33]
	Calcium carbonate[b)]	14	1.31 [1.09, 1.59]	1.25 [1.07, 1.46]
	Aluminum hydroxide, magnesium hydroxide, and simethicone[b), c)]	15	1.31 [1.09, 1.58]	1.22 [1.05, 1.42]
	Omeprazole[b)]	28	1.22 [1.05, 1.40]	1.07 [0.95, 1.20]

Geometric mean ratio [90% CI]

a) Danicopan alone was administered orally 3 times daily after meals on Days 1 to 4, and danicopan was coadministered with ciclosporin 300 mg on Day 5. The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}8h}$ of danicopan in the presence of ciclosporin" to "C_{max} or $AUC_{0\text{-}8h}$ of danicopan in the absence of ciclosporin."

b) Three administration methods were used.

Administration Method 1: Danicopan alone was orally administered 3 times daily after meals on Days 1 to 4, and danicopan was coadministered with calcium carbonate 1 g on Day 5.

Administration Method 2: Danicopan alone was orally administered 3 times daily after meals on Days 1 to 4, and danicopan was coadministered with aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 25 mg on Day 5.

Administration Method 3: On Days 1 to 4, danicopan alone was orally administered once daily. On Days 5 to 8, danicopan was administered orally 3 times daily after meals and omeprazole 40 mg orally once daily after a meal.

The washout period between the administration methods was ≥2 days. The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}8h}$ of danicopan in the presence of calcium carbonate, aluminum hydroxide/magnesium hydroxide/simethicone, or omeprazole" to "C_{max} or $AUC_{0\text{-}8h}$ of danicopan in the absence of the concomitant drugs."

c) Aluminum hydroxide, magnesium hydroxide, and simethicone were evaluated collectively as antacids.

6.2.11 Phase I study (drug interactions with warfarin, bupropion, ethinylestradiol, and norethisterone) (CTD 5.3.3.4-3: Study No. ACH471-017 [July to [redacted] 2019])

A study was conducted to investigate the effect of danicopan on the PK of warfarin (S-form [substrate of CYP2C9]), bupropion (substrate of CYP2B6), and ethinylestradiol and norethisterone (oral contraceptives) in non-Japanese healthy adults (target sample size, 52 subjects).

Table 29 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of warfarin, bupropion, and ethinylestradiol and norethisterone coadministered with danicopan to those of these drugs administered without danicopan.

Table 29. Geometric mean ratios (coadministration with danicopan/without danicopan) of plasma PK parameters of warfarin, bupropion, and ethinylestradiol and norethisterone

Danicopan (p.o.)	Concomitant drug	Analyte	N	C_{max}	$AUC_{0\text{-}inf}$
200 mg 3 times daily	Warfarin[a)]	R-warfarin	12	1.06 [1.02, 1.10]	1.03 [1.00, 1.06]
		S-warfarin	12	1.05 [0.99, 1.10]	1.14 [1.11, 1.17]
	Bupropion[a)]	Bupropion	16	1.05 [0.93, 1.19]	1.12 [1.06, 1.17]
		Hydroxy bupropion	16	0.93 [0.87, 0.98]	0.97 [0.92, 1.03]
	Ethinylestradiol and norethisterone[a)]	Ethinylestradiol	22	1.07 [1.00, 1.14]	1.24 [1.02, 1.50][b)]
		Norethisterone	22	1.13 [0.98, 1.31]	1.14 [1.02, 1.27]

Geometric mean ratio [90% CI]

a) The study consisted of 3 parts.

Part 1: In Period 1, warfarin 25 mg was administered as a single oral dose on Day 1. In Period 2, danicopan was administered orally 3 times daily after meals on Days 1 to 11, and warfarin 25 mg was coadministered with danicopan on Day 5. The washout period between Periods 1 and 2 was ≥14 days.

Part 2: In Period 1, bupropion 100 mg was administered as a single oral dose on Day 1. In Period 2, danicopan was administered orally 3 times daily after meals on Days 1 to 8, and bupropion 100 mg was coadministered with danicopan on Day 5. The washout period between Periods 1 and 2 was ≥7 days.

Part 3: In Period 1, ethinylestradiol 0.035 mg and norethisterone 1 mg were administered as a single oral dose on Day 1. In Period 2, danicopan was administered orally 3 times daily after meals on Days 1 to 8, and ethinylestradiol 0.035 mg and norethisterone 1 mg were coadministered with danicopan on Day 5. The washout period between Periods 1 and 2 was ≥7 days.

The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}inf}$ of warfarin, bupropion, and ethinylestradiol and norethisterone in the presence of danicopan" to "C_{max} or $AUC_{0\text{-}inf}$ of the drugs in the absence of danicopan."

b) 21 subjects

6.2.12 Phase I study (drug interactions with rosuvastatin) (CTD 5.3.3.4-4: Study No. ALXN2040-HV-102 [February to April 2023])

A study was conducted to investigate the effects of danicopan on the PK of rosuvastatin (substrate of BCRP and OATP1B1) in non-Japanese healthy adults (target sample size, 20 subjects).

Table 30 shows the geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ of rosuvastatin coadministered with danicopan to those of rosuvastatin administered without danicopan.

Table 30. Geometric mean ratios (coadministration with danicopan/without danicopan) of plasma PK parameters of rosuvastatin

Danicopan (p.o.)	Concomitant drug	N	C_{max}	$AUC_{0\text{-}inf}$
200 mg 3 times daily	Rosuvastatin[a)]	18	3.29 [2.76, 3.92]	2.25 [2.05, 2.46]

Geometric mean ratio [90% CI]

a) In Period 1, rosuvastatin 20 mg was administered as a single oral dose on Day 1. In Period 2, danicopan 200 mg was administered orally 3 times daily on Days 1 to 7, and rosuvastatin 20 mg was coadministered with danicopan on Day 4. The washout period between Periods 1 and 2 was ≥5 days. The geometric mean ratio is the ratio of "C_{max} or $AUC_{0\text{-}inf}$ of rosuvastatin in the presence of danicopan" to " C_{max} or $AUC_{0\text{-}inf}$ of rosuvastatin in the absence of danicopan."

6.2.13 Phase I study (QT/QTc assessment) (CTD 5.3.3.1-5: Study No. ACH471-013 [July to October 2018])

A placebo- and active-controlled, randomized, double-blind study was conducted at 1 foreign study site to investigate the effect on the QT/QTc interval following a single oral dose of danicopan in non-Japanese healthy adults (target sample size, 33 subjects [9 in the danicopan group and 24 in the control group]).

All of 33 subjects who received the study drug were included in the QTc analysis population, the safety analysis population, and the PK analysis population.

Placebo, danicopan (at escalating doses of 400, 800, and 1,200 mg), or the positive control moxifloxacin 400 mg was administered as a single oral dose under fasted conditions.

The maximum ΔΔQTcF (upper limit of the 1-sided 90% CI) following administration of danicopan 400, 800, and 1,200 mg was 2.9 (7.1), 5.2 (8.5), and 1.7 (6.2) ms, respectively. The maximum ΔΔQTcF (90% CI) in the moxifloxacin group was 13.9 [11.3, 16.5] ms, and the lower limit of the 90% CI was higher than 5 ms. The analytical sensitivity was therefore considered to be appropriate.

Table 31 shows plasma PK parameters of danicopan following a single oral dose of danicopan 400, 800, or 1,200 mg; the exposure levels exceeded the estimated exposure levels at the maximum clinical dose (200 mg 3 times daily) (Table 32).

In view of the above, the applicant explained that the risk of QT prolongation was considered to be clinically insignificant.

Table 31. Plasma PK parameters of danicopan following a single oral dose of danicopan

Danicopan dose	N	C_{max} (ng/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (ng·h/mL)
400 mg	9	535 ± 60	3.0 (1.0, 4.1)	3,320 ± 54
800 mg	9	870 ± 57	2.0 (1.0, 4.0)	5,856 ± 40
1,200 mg	9	1,027 ± 47	2.5 (1.0, 8.0)	8,094 ± 48

Mean ± standard deviation
a) Median (minimum, maximum)

As for safety, adverse events were observed in 25.0% (6 of 24) of subjects in the placebo treatment period, 16.7% (4 of 24) of subjects in the moxifloxacin treatment period, and 22.2% (2 of 9) of subjects in the danicopan 1,200 mg treatment period. A serious adverse event was observed in 1 subject (pneumonia) in the placebo treatment period, and adverse events leading to treatment discontinuation in 2 subjects (blood creatine phosphokinase increased and pneumonia in 1 subject each) in the placebo treatment period. All of the events were unrelated to the study drug. There were no adverse drug reactions or adverse events that resulted in death.

6.2.14 Population PK analysis (CTD 5.3.3.5-2)

Population PK analysis was performed (software: NONMEM Version 7.5.0) using the PK data of danicopan (407 subjects treated with danicopan, at 7,195 time points) obtained in phase I studies in healthy adults (Studies ACH471-001,[39)] ACH471-002, ACH471-006,[40)] ACH471-009, ACH471-010, ACH471-012, ACH471-013, ACH471-014, ACH471-016, ACH471-017, and ALXN2040-HV-101), and phase II studies (Studies ACH471-100[41)] and ACH471-101) and a phase III study (Study ALXN2040-PNH-301) in patients with PNH.

[39)] A placebo-controlled, randomized, double-blind study to investigate the PK and safety of danicopan administered as a single oral escalating dose in non-Japanese healthy adults
[40)] A randomized, open-label, crossover study to evaluate the relative bioavailability of the tablet and soft gel formulations of danicopan to the liquid-filled capsule formulation in non-Japanese healthy adults
[41)] A foreign phase II study of danicopan monotherapy in treatment-naïve patients with PNH

As the base model, a 2-compartmental model with zero-order release, first-order absorption, and first-order elimination was constructed, including the following covariates: [1] formulation and meals, [2] formulation and meals, [3] formulation, dose, and meals, [4] body weight, sex, and renal impairment, [5] body weight, and [6] body weight, respectively, for [1] absorption rate constant (ka), [2] zero-order release time, [3] bioavailability, [4] CL/F, [5] Q/F, and [6] Vc/F and Vp/F.

As a result of investigation of the covariates,[42] the following covariates were included in the final model: [1] formulation and meals, [2] formulation and meals, [3] formulation, dose, and meals, [4] body weight, sex, and renal impairment, [5] body weight, and [6] body weight, respectively, for [1] ka, [2] zero-order release time, [3] bioavailability, [4] CL/F, [5] Q/F, and [6] Vc/F and Vp/F of danicopan. Table 32 shows the estimated C_{max}, AUC, and C_{trough} of danicopan at steady state following oral doses of danicopan 150 or 200 mg 3 times daily in patients with PNH in each body weight category.

Table 32. PK parameters of danicopan following multiple oral doses of danicopan in patients with PNH by body weight category

Dosage regimen of danicopan	Body weight category	N	$C_{max,ss}$ (ng/mL)	$AUC_{0\text{-}24h,ss}$ (ng·h/mL)	$C_{trough,ss}$ (ng/mL)
150 mg 3 times daily	Entire population	69	558 ± 172	8,350 ± 2,420	169 ± 68
	>40 kg and ≤60 kg	21	674 ± 143	10,100 ± 2,070	203 ± 70
	>60 kg and ≤100 kg	44	509 ± 159	7,640 ± 2,150	156 ± 64
	>100 kg and ≤150 kg	4	481 ± 174	6,940 ± 2,340	133 ± 49
200 mg 3 times daily	Entire population	69	694 ± 214	10,400 ± 3,010	211 ± 85
	>40 kg and ≤60 kg	21	839 ± 178	12,600 ± 2,580	253 ± 87
	>60 kg and ≤100 kg	44	634 ± 198	9,510 ± 2,680	195 ± 79
	>100 kg and ≤150 kg	4	599 ± 216	8,650 ± 2,920	166 ± 61

Mean ± standard deviation

6.R Outline of the review conducted by PMDA

PMDA's conclusion:

On the basis of the data submitted and the results of the investigations in Sections 6.R.1 to 6.R.5, it is reasonable to list drugs serving as a substrate of P-gp and BCRP under "Precautions for Concomitant Use." In view of the observed effect of food, it is appropriate to specify that danicopan should be administered under fed conditions under "Dosage and Administration."

6.R.1 Differences in the PK of danicopan in Japanese and non-Japanese populations

The applicant's explanation about the PK of danicopan in Japanese and non-Japanese populations:

In Studies ALXN2040-HV-101 and ACH471-016 in healthy adults, the mean C_{max} and $AUC_{0\text{-}inf}$ following a single oral dose of danicopan under fasted conditions were higher in Japanese subjects than in non-Japanese subjects by 36% and 9%, respectively. In the population PK analysis, C_{max} was estimated to increase with

[42] The following covariates for CL/F, Vc/F, bioavailability, ka, and T_{lag} of danicopan were investigated:
CL/F: age, body weight, sex, race, country or region (Japanese vs non-Japanese, East Asia vs non-East Asia), presence/absence of hepatic impairment, AST, ALT, total bilirubin, albumin concentration, creatinine clearance or renal impairment category, population (healthy adults, patients with PNH), baseline complement D concentration, and concomitant drug (eculizumab, ravulizumab, no concomitant drug)
Vc/F: age, body weight, sex, race, country or region (Japanese vs non-Japanese, East Asia vs non-East Asia), population (healthy adults, patients with PNH), and baseline complement D concentration
Bioavailability: danicopan dose, meal (fasted, standard diet, high-fat diet), and formulation (tablet, capsule)
ka: meal (fasted, standard diet, high-fat diet) and formulation (tablet, capsule)
T_{lag}: meal (fasted, normal diet, high-fat diet) and formulation (tablet, capsule)

decreasing body weight and to be 31% higher in female than male subjects [see Section 6.2.14]. The mean body weight (63.6 kg in Japanese subjects and 76.7 kg in non-Japanese subjects) and the percentage of female subjects (56% in Japanese subjects and 22% in non-Japanese subjects) differed between the Japanese and non-Japanese subpopulations in Studies ALXN2040-HV-101 and ACH471-016, and this is considered to be a cause of difference in exposure between the two subpopulations. Following a single oral dose of danicopan under fed conditions, there were no clear differences in the C_{max} or $AUC_{0\text{-}inf}$ of danicopan between Japanese and non-Japanese subjects [see Section 6.2.1 and 6.2.2].

In the global phase III study (Study 301), the mean C_{trough} of danicopan at Weeks 16 and 24 in patients with PNH tended to be higher in the Japanese subpopulation than in the non-Japanese subpopulation [see Section 6.2.8] in both treatment groups. The difference in mean body weight between the Japanese and non-Japanese subpopulations in Study 301 (61.0 kg in Japanese subjects and 71.9 kg in non-Japanese subjects) was considered to be a cause of difference in exposure between the 2 subpopulations. However, individual changes in plasma danicopan concentration in Japanese subjects were within the range of distribution of those in non-Japanese subjects, suggesting that there are no clear differences between the Japanese and non-Japanese populations.

PMDA's view:
As for the PK of danicopan, the mean exposure tended to be higher in Japanese subjects than in non-Japanese subjects in all studies. The appropriateness of the proposed dosage and administration in Japanese patients is discussed in Section 7, based on the efficacy and safety results of the global phase III study and other data.

6.R.2 Administration timing

The applicant's explanation about the administration timing of danicopan:
Since continuous exposure to danicopan is required to ensure the exertion of its pharmacological effects, the efficacy of danicopan is considered more related to AUC than to C_{max}. The population PK analysis [see Section 6.2.14] suggested that the $AUC_{0\text{-}24h,ss}$ of danicopan 150 mg orally administered 3 times daily under fasted conditions was approximately 13% lower than that under fed conditions. On the other hand, the investigation of the relationship between the efficacy and $AUC_{0\text{-}24h,ss}$ of danicopan following multiple oral doses under fed conditions in Study 301 showed no clear correlation between the "change in Hb level from baseline to Week 12" and the $AUC_{0\text{-}24h,ss}$ of danicopan. The population PK analysis estimated that C_{max} under fasted conditions was approximately 8% lower than that after intake of a standard diet, and the investigation of the relationship between the efficacy and C_{max} of danicopan following multiple oral doses under fed conditions in Study 301 showed a relatively flat relationship between the "change in Hb level from baseline to Week 12" and the C_{max} of danicopan; this suggests that an approximately 8% decrease in C_{max} does not significantly affect the efficacy of danicopan.

In view of the above, the C_{max} and $AUC_{0\text{-}24h,ss}$ of danicopan administered under fasted conditions are estimated to be lower by approximately 8% and approximately 13%, respectively, than those administered after intake of a standard diet. However, this difference does not significantly affect the efficacy of danicopan, and

danicopan administered under fasted condition is expected to have similar efficacy as danicopan administered under fed conditions. The administration timing with respect to meal conditions was therefore not specified in the proposed dosage and administration.

PMDA's view:

Study ACH471-016 revealed a food effect, namely C_{max} of danicopan administered under fasted conditions was approximately half that administered after a high-fat diet. The applicant explained that C_{max} of danicopan was not related to its efficacy, but it is unclear to which extent changes in danicopan exposure affect its efficacy. The global phase III study of danicopan evaluated its efficacy and safety under fed conditions as per the study protocol; the study therefore does not provide sufficient data for fully determining the efficacy under decreased exposure to danicopan administered under fasted conditions. It is thus appropriate to require that danicopan be administered under fed conditions in the "Dosage and Administration" section of the package insert.

6.R.3 Effect of renal impairment on the PK of danicopan

The applicant's explanation about the effect of renal impairment on the PK of danicopan:

In the PK evaluation of danicopan in subjects with severe renal impairment in Study ACH471-009, the geometric mean $AUC_{0\text{-}inf}$ of danicopan in subjects with severe renal impairment was 1.52 times that in subjects with normal renal function. None of the adverse events observed in ≥5% of subjects in Study 301 in patients with PNH showed an obviously increased incidence in the subgroup of subjects with high $AUC_{0\text{-}24h,ss}$. In Study 301, the dose of danicopan was increased to 200 mg in 71.9% (41 of 57) of subjects with normal renal function, 76.9% (10 of 13) of patients with mild renal impairment, and 61.5% (8 of 13) of patients with moderate renal impairment; the percentage was similar regardless of the presence, absence, or severity of renal impairment. Table 33 shows the incidence of adverse events by renal function. While serious adverse events tended to be more common in patients with moderate renal impairment, the incidence of adverse drug reactions and adverse events leading to treatment discontinuation was similar regardless of the presence, absence, or severity of renal impairment.

Table 33. Incidence of adverse events by renal function following an oral dose of danicopan in patients with PNH

	Normal[a)] (N = 57)	Mild impairment[b)] (N = 13)	Moderate impairment[c)] (N = 13)
All adverse events	96.5 (55)	92.3 (12)	92.3 (12)
All adverse drug reactions	24.6 (14)	30.8 (4)	23.1 (3)
Serious adverse events	14.0 (8)	23.1 (3)	38.5 (5)
Serious adverse drug reactions	3.5 (2)	0	0
Adverse events leading to treatment discontinuation	5.3 (3)	0	15.4 (2)
Adverse drug reactions leading to treatment discontinuation	3.5 (2)	0	15.4 (2)

Incidence % (n)

a) eGFR >90 mL/min/1.73 m^2

b) eGFR ≥60 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2

c) eGFR ≥30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2

The population PK analysis also estimated that the $AUC_{0\text{-}24h,ss}$ of danicopan (mean ± standard deviation) in subjects with normal renal function (42 subjects), patients with mild renal impairment (14 subjects), and

patients with moderate renal impairment (13 subjects) in Study 301 was 8,210 ± 2,270 ng·h/mL, 8,580 ± 3,010 ng·h/mL, and 8,590 ± 2,380 ng·h/mL, respectively, at 150 mg, and 10,200 ± 2,820 ng·h/mL, 10,700 ± 3,750 ng·h/mL, and 10,700 ± 2,960 ng·h/mL, respectively, at 200 mg; this suggests that the exposure to danicopan is similar at both doses regardless of the presence, absence, or severity of renal impairment.

These results showed that danicopan exposure tended to be higher in patients with severe renal impairment than in subjects with normal renal function, but the presence, absence, or severity of renal impairment was not considered to affect the dose increases or safety of danicopan. The applicant therefore considers it unnecessary to provide precautions regarding danicopan treatment in patients with mild, moderate, or severe renal impairment in the package insert.

PMDA's view:
In a phase I study, which investigated the effect of renal impairment on the PK of danicopan (Study ACH471-009), the $AUC_{0\text{-}inf}$ of danicopan was higher in subjects with severe renal impairment than in subjects with normal renal function. Precautionary statements should be included in the package insert, etc. to ensure that the condition of patients who receive danicopan is carefully monitored if they have severe renal impairment, for the following reasons: (a) Exposure to danicopan may increase in patients with PNH with severe renal impairment; (b) the safety in such patients has not been confirmed because they were not enrolled in the global phase III study in patients with PNH (Study 301). In patients with mild or moderate renal impairment, the estimated $AUC_{0\text{-}24h,ss}$ of danicopan at the clinical dose did not clearly differ from that in subjects with normal renal function, and no clinically significant trend in safety was observed, although there are limitations to the evaluation due to the extremely limited number of subjects studied in the phase III study (Study 301). The applicant's proposal not to provide precautions for patients with PNH with mild or moderate renal impairment in the package insert, is appropriate.

6.R.4 Interactions mediated by P-gp

The applicant's explanation about interactions mediated by P-gp:
The investigation of the effect of coadministered danicopan 150 mg on the PK of fexofenadine in Study ACH471-010 showed that the C_{max} and $AUC_{0\text{-}inf}$ of fexofenadine increased 1.42 and 1.62 times, respectively, in the presence of coadministered danicopan [see Section 6.2.9]. Danicopan inhibited OAT3, OATP1B1, OATP1B3, MATE1, and MATE2-K in *in vitro* studies. Although fexofenadine is a substrate of these transporters, investigation based on the drug interaction guideline suggested that danicopan was unlikely to cause drug interactions mediated by OAT3, OATP1B1, OATP1B3, MATE1, or MATE2-K. The increase in exposure to fexofenadine in Study ACH471-010 was therefore probably attributed mainly to the P-gp inhibitory effect of danicopan. The investigation of the effect of coadministered danicopan 200 mg on the PK of tacrolimus in Study ACH471-014 showed that the C_{max} and $AUC_{0\text{-}inf}$ of tacrolimus increased 1.13 and 1.49 times, respectively, in the presence of coadministered danicopan [see Section 6.2.10]. Tacrolimus is a substrate of both CYP3A and P-gp; the increased exposure to tacrolimus was considered due mainly to the P-gp inhibitory effect of danicopan, in view of that coadministration of danicopan with the CYP3A substrate midazolam resulted in a <25% increase in the C_{max} and $AUC_{0\text{-}inf}$ of midazolam.

In view of the above, coadministration of danicopan with drugs serving as a substrate of P-gp may increase exposure to these drugs. The applicant therefore considers it appropriate to list drugs serving as a substrate of P-gp under "Precautions for Concomitant Use" in the package insert.

PMDA considers that the investigations conducted by the applicant and interpretation of the results are appropriate, and that the applicant's explanation that drugs serving as a substrate of P-gp will be listed under "Precautions for Concomitant Use" is appropriate.

6.R.5 Interactions mediated by BCRP

The applicant's explanation about interactions mediated by BCRP:

The investigation of the effect of coadministered danicopan 200 mg on the PK of rosuvastatin in Study ALXN2040-HV-102 showed that the C_{max} and $AUC_{0\text{-}inf}$ of rosuvastatin increased 3.29 and 2.25 times, respectively, in the presence of coadministered danicopan [see Section 6.2.12]. Danicopan inhibited P-gp and OATP1B1 in *in vitro* studies. Although rosuvastatin is a substrate of these transporters, the increase in exposure to rosuvastatin was considered due mainly to inhibition of BCRP by danicopan, for the following reasons:

(a) There is no report stating that P-gp obviously affects the PK of rosuvastatin during its clinical use.
(b) Investigation based on the drug interaction guideline suggested that danicopan was unlikely to cause drug interactions associated with its inhibition of OATP1B1.

The applicant therefore considers that drugs serving as a substrate of BCRP should be listed under "Precautions for Concomitant Use" in the package insert.

PMDA considers that the investigations conducted by the applicant and the interpretation of the results are appropriate, and that the applicant's proposal to list drugs serving as a substrate of BCRP under "Precautions for Concomitant Use" is appropriate.

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

The applicant submitted results from 1 foreign phase II study and 1 global phase III study as main data for evaluating the efficacy and safety (Table 34).

Table 34. Outline of main clinical studies on efficacy and safety

Phase	Study No.	Population	Study design	Group, No. of subjects, dose, administration period	Primary efficacy endpoint
Foreign Phase II	ACH 471-101	Patients with PNH with an inadequate response to eculizumab	Open-label Uncontrolled	• Primary evaluation period (24 weeks): 12 subjects Danicopan 100-150 mg TID, p.o. Dose can be increased to up to 200 mg TID. • Extension period: 11 subjects (≥3 years in all subjects, 233 weeks at the longest) Danicopan was continued at the same dose as at the end of primary evaluation period.	Change in Hb level from baseline to Week 24
Global Phase III	ALXN2040 -PNH-301	Patients with PNH with an inadequate response to ravulizumab or eculizumab	Randomized Double-blind Placebo-controlled	• Double-blind period (12 weeks): Placebo group: 29 subjects (4 Japanese subjects) Danicopan group: 57 subjects (8 Japanese subjects) Placebo or danicopan 150 mg TID, p.o. (Dose can be increased to up to 200 mg TID.) • Continued treatment period (12 weeks): 71 subjects Subjects in the placebo group switched to danicopan. Subjects in the danicopan group continued danicopan. • Extension period (up to 2 years): 60 subjects Danicopan was continued at the same dose as at Week 24.	Change in Hb level from baseline to Week 12

7.1 Phase II study

7.1.1 Foreign phase II study (CTD 5.3.5.2.2: Study No. ACH471-101 [May 2018 to January 2023])

A multicenter, open-label, uncontrolled study was conducted at 5 study sites in 3 foreign countries to investigate the efficacy and safety of danicopan in patients with PNH with an inadequate response to eculizumab (Table 35). (target sample size, 14 subjects[43)])

Table 35. Main inclusion/exclusion criteria

Main inclusion criteria
- Patients aged ≥18 to ≤65 years
- Patients diagnosed with PNH
- Patients with absolute reticulocyte count ≥100 × 10^9/L and Hb <10 g/dL
- Patients who received ≥1 red blood cell transfusion within 12 weeks before screening
- Patients who received eculizumab for ≥24 weeks without changes to the dose or schedule in the previous ≥8 weeks
- Patients with platelet count ≥40,000/μL who did not require platelet transfusion
- Patients who had previously been vaccinated against *Meningococcus*, *Haemophilus influenzae*, or *Pneumococcus*, or were willing to receive protocol-specified vaccines

Main exclusion criteria
- Patients with complement C5 mutation
- Patients with confirmed or suspected complement deficiency
- Patients with past history of meningococcal infection, or who had contact with a first-degree relative or family member with a past history of meningococcal infection

This study consisted of 4 treatment groups (Groups 1-4), and included a primary evaluation period (subjects received oral danicopan in combination with intravenous eculizumab[44)] for 24 weeks) and an extension period[45)] (subjects who clinically responded to danicopan in the primary evaluation period were allowed to continue danicopan at the same dose as at the end of the primary evaluation period). Table 36 shows the starting

43) Since patients with PNH with an inadequate response to eculizumab are limited, the sample size was set as 14 subjects to ensure the feasibility of exploring the optimal dose of danicopan in combination with eculizumab.
44) Each patient received eculizumab at their usual dose according to their usual dosing schedule.
45) In the extension period, subjects were allowed to continue danicopan until any of the following events were confirmed: [1] Launch of danicopan in the country of the subject's residence; [2] Termination of development of danicopan as a potential treatment for PNH; [3] Intolerability to treatment or loss of treatment effect; [4] Participation in another clinical study conducted by the sponsor; [5] The investigator judged that alternative treatment is available.

dose of danicopan.[46)] Subjects were enrolled in the study sequentially from Group 1 to Group 4, and dose increase to 200 mg 3 times daily (TID) was allowed based on discussion between the investigator and the sponsor.

Table 36. Starting dose in each group

	Starting dose
Group 1	100 mg TID
Group 2	150 mg TID
Group 3	100 mg TID
Group 4	100 mg TID

A total of 12 subjects were enrolled in the study, consisting of 3 in Group 1, 2 in Group 2, 3 in Group 3, and 4 in Group 4. All 12 enrolled subjects received the study drug and were included in the safety analysis population. Of them, 11 subjects who received danicopan for ≥4 weeks were included in the modified intent to treat (mITT) population and the efficacy analysis population. One subject discontinued the treatment (adverse events) in the primary evaluation period, and 11 subjects completed the primary evaluation period and entered the extension period.

The starting dose was 100 mg TID in 10 subjects and 150 mg TID in 2 subjects. Table 37 shows dose changes after the start of treatment.

Table 37. Dose adjustment in each patient

Starting dose	Changes	N
100 mg TID (10 subjects)	Increased to 200 mg TID	6
	Increased to 150 mg TID	2
	Increased to 150 mg TID → reduced to 100 mg TID → increased to 200 mg TID	1
	Discontinued due to adverse events	1
150 mg TID (2 subjects))	Continued at 150 mg	1
	Increased to 200 mg TID	1

As for efficacy, the change (mean ± standard deviation) in Hb level from baseline to Week 24, assessed as the primary endpoint, was 2.39 ± 1.33 g/dL (Table 38).

Table 38. Change in Hb level (g/dL) from baseline to Week 24 (mITT)

	Danicopan (11 subjects)
Hb level at baseline[a)]	7.94 ± 1.43
Hb level at Week 24	10.33 ± 1.66
Change in Hb level from baseline[a)] to Week 24[b)]	2.39 ± 1.33

Mean ± standard deviation

a) At the start of the primary evaluation period

b) Summary statistics of the change from baseline in Hb level in all patients assigned to each group

As for safety, adverse events were observed in 100% (12 of 12) of subjects in the primary evaluation period. Adverse events observed in ≥2 subjects were upper respiratory tract infection in 5 subjects, headache in 3

[46)] Subjects in Groups 2 and 3 were allowed to use lower starting doses than the original starting doses determined when the study was planned (original starting doses: 150 mg TID and 200 mg TID, respectively) based on the safety data obtained from their respective preceding groups (starting doses: 100 mg TID in Group 1 and 150 mg in Group 2). The optimal starting dose in Group 4 was to be determined based on the safety data from Groups 1 to 3. Eventually, the starting dose in Groups 3 and 4 were determined to be 100 mg TID.

subjects, and arthralgia, musculoskeletal pain, pain in extremity, abdominal discomfort, abdominal pain, nausea, fatigue, non-cardiac chest pain, vaccination site pain, neutropenia, ALT increased, anxiety, and contusion in 2 subjects each. Adverse drug reactions were observed in 16.7% (2 of 12) of subjects (ALT increased and sinus tachycardia in 1 subject each). There were no deaths. While serious adverse events were observed in 16.7% (2 of 12) of subjects (pneumonia and pulmonary oedema in 1 subject each), there were no serious adverse drug reactions. The only adverse event leading to discontinuation of danicopan treatment was pulmonary oedema in 1 subject.

In the extension period, adverse events were observed in 100% (11 of 11) of subjects. Adverse events observed in ≥2 subjects were COVID-19 in 6 subjects, upper respiratory tract infection, headache, and pyrexia in 5 subjects each, fatigue and influenza like illness in 3 subjects each, and conjunctivitis, nasopharyngitis, sinusitis, pain, arthralgia, limb discomfort, myalgia, pain in extremity, anosmia, thrombocytopenia, cough, oropharyngeal pain, insomnia, and haemoglobinuria in 2 subjects each. Adverse drug reactions were observed in 18.2% (2 of 11) of subjects (ALT increased, pyrexia, and immunisation reaction in 1 subject each [1 subject developed ≥1 event]). There were no deaths. Serious adverse events were observed in 63.6% (7 of 11) of subjects (pyrexia, device related infection, febrile neutropenia, influenza like illness, pyelonephritis, schwannoma, haemoglobinuria, haemolysis, pancreatitis, and tracheobronchitis viral in 1 subject each [some subjects developed ≥1 event]). Of these, pyrexia was assessed as an adverse drug reaction, but the event resolved. There were no reports of meningococcal infection throughout the period.

7.2 Phase III study

7.2.1 Global phase III study (CTD 5.3.5.1.1: Study No. ALXN2040-PNH-301 [[redacted] 20[redacted] to data cut-off for interim analysis of June 28, 2022, data cut-off of [redacted], [redacted] for additional analysis [1], and data cut-off of March 31, 2023 for additional analysis [2]; ongoing as of [redacted] 20[redacted]])

A multicenter, placebo-controlled, randomized, double-blind, parallel-group study was conducted at 80 study sites in 18 countries, including Japan, to investigate the efficacy and safety of danicopan in patients with PNH with an inadequate response to ravulizumab or eculizumab (both complement C5 inhibitors) (Table 39) (target sample size, 84 subjects[47)]).

[47)] A sample size of 84 subjects was required to ensure a statistical power of 99% to show a clinically meaningful 2 g/dL treatment difference between the danicopan and placebo groups in the mean change in Hb level from baseline to Week 12 (the primary endpoint), in 2-sided t-test at 0.05 significance level, assuming a standard deviation of 1.6 g/dL based on the results of Study ACH471-101, an allocation ratio (danicopan : placebo) of 2:1 and a drop-out rate of approximately 10%.

Table 39. Main inclusion/exclusion criteria

Main inclusion criteria • Patients aged ≥18 years • Patients diagnosed with PNH • Patients with absolute reticulocyte count ≥120 × 10^9/L and Hb ≤9.5 g/dL • Patients receiving a complement C5 inhibitor (ravulizumab or eculizumab) at the approved or a higher dose for ≥6 months without changes to the dose or dosing interval • Patients with platelet count ≥30,000/μL who did not require platelet transfusion • Patients with absolute neutrophil count ≥500/μL • Patients who received meningococcal vaccination within the past 3 years or at the start of study treatment Main exclusion criteria • Patients with confirmed or suspected complement deficiency • Patients with ALT >2 × upper limit of normal (ULN) (>3 × ULN for patients with serum ferritin ≥500 ng/mL) • Patients with direct bilirubin >2 × ULN • Patients with eGFR <30 mL/min/1.73 m^2 or on dialysis

This study consisted of the following 3 parts: a double-blind period of 12 weeks (subjects were randomized to placebo or danicopan in a 1:2 ratio), a continued treatment period of 12 weeks (subjects in the placebo group switched to danicopan and those in the danicopan group continued danicopan), and an extension period of up to 2 years (all subjects entered the extension period and received danicopan at the same dose as at Week 24). In all periods, ravulizumab or eculizumab was continuously administered. Placebo or danicopan 150 mg was orally administered TID, and dose increase to up to 200 mg TID was allowed according to the dose increase criteria shown in Table 40.[48)]

Table 40. Dose increase criteria

Timing of dose increase	Condition for dose increase
Week 6	Hb at Week 4 has not increased by ≥2 g/dL from baseline, or the subject has received blood transfusion in the past 4 weeks.
Week 12	Hb at Week 10 has not recovered to the median value of the reference range by sex from baseline, or the subject has received blood transfusion in the past 4 weeks.
Week 18	Hb at Week 16 has not recovered to the median value of the reference range by sex from baseline, or the subject has received blood transfusion in the past 4 weeks.
Week 24	The subject has not received 200 mg TID but received the same dose for ≥4 weeks.

The following interim analysis and additional analyses were performed in this study:

- Interim analysis (data cut-off: June 28, 2022)

  This interim analysis was pre-specified in the protocol and performed when 75% (63 subjects) of the target sample size (84 subjects)[49)] completed the double-blind period at Week 12. The primary endpoint and key secondary endpoints at Week 12 were assessed by the Data Monitoring Committee (DMC) under open-label conditions, and the efficacy results were favorable. Accordingly, the sponsor was unblinded on [redacted], 20[redacted] as recommended by the DMC according to the prescribed plan. The investigators and patients remained blinded until additional analysis [1].

48) The protocol Version 3 and earlier versions stated that "Treatment should be started at 100 mg TID in patients with ALT or direct bilirubin of >1.5 × ULN at screening." However, as a result of review of safety, PK, PD, and efficacy data in the foreign phase II studies of danicopan in patients with PNH or patients with complement 3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis (Studies ACH471-101, ACH471-103, ACH471-204, and ACH471-205), a starting dose of 150 mg TID was considered to be appropriate. In the protocol Version 4 and later versions, "the starting dose of 100 mg TID" was deleted and replaced by "the starting dose of 150 mg TID in all subjects." When the protocol was revised to Version 4, 3 subjects were receiving danicopan 100 mg TID; their dose was increased to 150 mg TID.

49) The interim analysis was to be performed when approximately 75% (63 subjects) of the target sample size (84 subjects) had completed or discontinued the double-blind period (12 weeks) to consider early termination for efficacy. The 2-sided significance level used for the primary endpoint was calculated to be 0.018 for interim analysis and 0.046 for final analysis according to the α-spending function ($\gamma = -4$) of Hwang-Shih-DeCani. The 2-sided significance level used for key secondary endpoints was calculated to be 0.042 for interim analysis and 0.024 for final analysis according to the α-spending function ($\gamma = 1$) of Hwang-Shih-DeCani. The type I error rate of the study was controlled within 5% by using a fixed sequence procedure for the primary endpoint and key secondary endpoints.

- Additional analysis [1] (data cut-off: [redacted], 20[redacted])
  As instructed by the U.S. Food and Drug Administration (FDA), an efficacy analysis that had not been pre-specified was performed in the 63 subjects included in the interim analysis for efficacy when they completed the continued treatment period at Week 24. Safety analysis was also performed in all 86 subjects who had been enrolled at the time of data cut-off.
- Additional analysis [2] (data cut-off: March 31, 2023)
  Data cut-off was performed to analyze long-term safety data. Safety analysis that had not been pre-specified was performed in 84 danicopan-treated subjects among the 86 subjects who received the study drug at the time of data cut-off.

This study enrolled 86 patients with PNH with an inadequate response to ravulizumab or eculizumab. The 86 enrolled patients were randomized in a 1:2 ratio to placebo or danicopan, resulting in the assignment of 29 subjects (including 4 Japanese subjects) to the placebo group and 57 subjects (including 8 Japanese subjects) to the danicopan group. All subjects received the study drug and were included in the safety analysis population (Interim Safety Analysis Set). Of the randomized subjects, 21 (including 2 Japanese subjects) in the placebo group and 42 (including 5 Japanese subjects) in the danicopan group at the time of interim analysis were included in the primary efficacy analysis population (Interim Efficacy Analysis Set). As instructed by the FDA, efficacy analysis was performed again on the 63 subjects analyzed for efficacy in the interim analysis when they completed the continued treatment period at Week 24 (additional analysis [1]).

At the time of additional analysis [2], 4 subjects had discontinued treatment in the double-blind period, namely, 2 subjects in the placebo group (adverse events and subject's withdrawal of consent in 1 subject each) and 2 subjects in the danicopan group (adverse events in both subjects). The remaining 27 subjects in the placebo group (placebo/danicopan group) and 55 subjects in the danicopan group (continued danicopan group) entered the extension period. In the continued treatment period, 2 subjects discontinued treatment, namely, 1 subject in the placebo/danicopan group (adverse events) and 1 subject in the continued danicopan group (adverse events). The remaining 26 subjects in the placebo/danicopan group and 54 subjects in the continued danicopan group entered the extension period. As of the data cut-off of March 31, 2023, 7 subjects had discontinued treatment, namely, 1 subject in the placebo/danicopan group (adverse events) and 6 subjects in the continued danicopan group (subject's withdrawal of consent in 3, investigator's judgment in 2, and non-compliance with study treatment in 1 subject).

The efficacy results of Study 301 from additional analysis [1] are presented below, with the safety results from additional analysis [2]. The efficacy results during the double-blind period did not differ between the additional analysis [1] and the interim analysis.

As for efficacy, the primary endpoint "change in Hb level from baseline to Week 12" (least squares mean ± standard error) (Interim Efficacy Analysis Set) was 2.94 ± 0.21 g/dL in the danicopan group and 0.50 ± 0.31 g/dL in the placebo group, with an intergroup difference of 2.44 ± 0.38 g/dL. This showed the superiority

of danicopan over placebo (P < 0.0001, mixed-effects model for repeated measures [MMRM], 2-sided significance level 0.018).[50)]

Table 41. Change in Hb level (g/dL) from baseline to Week 12 (Double-blind period: Interim Efficacy Analysis Set)

	Placebo (21 subjects)	Danicopan (42 subjects)
Hb level at baseline (mean ± standard deviation)	7.74 ± 1.04	7.66 ± 0.94
Change in Hb level from baseline to Week 12 (mean ± standard deviation)	0.65 ± 0.91 (20 subjects)	3.15 ± 1.27 (36 subjects)
Change in Hb level from baseline to Week 12 (least squares mean ± standard error)[a)]	0.50 ± 0.31	2.94 ± 0.21
Intergroup difference (danicopan – placebo) [95%CI][a)]	2.44 [1.69, 3.20]	
P value[a) b)]	<0.0001	

a) Calculated by MMRM with treatment group, visit timing, interaction between visit timing and treatment group, baseline Hb, and prior blood transfusion as explanatory variables and assuming an unstructured covariance matrix.
b) Two-sided significance level 0.018

As for safety, Table 42 shows a summary of adverse events. Adverse events were observed in 62.1% (18 of 29) of subjects in the placebo group and 75.4% (43 of 57) of subjects in the danicopan group in the double-blind period, 66.7% (18 of 27) of subjects in the placebo/danicopan group[51)] and 72.7% (40 of 55) of subjects in the continued danicopan group in the continued treatment period, and 84.6% (22 of 26) of subjects in the placebo/danicopan group and 75.9% (41 of 54) of subjects in the continued danicopan group in the extension period. Adverse drug reactions were observed in 27.6% (8 of 29) of subjects in the placebo group and 21.1% (12 of 57) of subjects in the danicopan group in the double-blind period, 25.9% (7 of 27) of subjects in the placebo/danicopan group and 5.5% (3 of 55) of subjects in the continued danicopan group in the continued treatment period, and 15.4% (4 of 26) of subjects in the placebo/danicopan group and 3.7% (2 of 54) of subjects in the continued danicopan group in the extension period.

[50)] The least squares mean of the "change in Hb level from baseline to Week 12" (the primary efficacy endpoint) was analyzed using MMRM. In this model, treatment group, visit, interaction between treatment group and visit, baseline Hb, and prior blood transfusion (which was a randomization stratification factor) were defined as explanatory variables. Hb levels measured within 4 weeks after blood transfusion were not included in the model.
[51)] Group of subjects who received placebo in the double-blind period and switched to danicopan in the continued treatment period.

Table 42. Summary of adverse events by part (Safety Analysis Set, additional analysis [2])

	Double-blind period (12 weeks)		Continued treatment period (12 weeks)		Extension period (Up to 2 years)	
	Placebo (N = 29)	Danicopan (N = 57)	Placebo/ danicopan (N = 27)	Continued danicopan (N = 55)	Placebo/ danicopan (N = 26)	Continued danicopan (N = 54)
All adverse events	62.1 (18)	75.4 (43)	66.7 (18)	72.7 (40)	84.6 (22)	75.9 (41)
All adverse drug reactions	27.6 (8)	21.1 (12)	25.9 (7)	5.5 (3)	15.4 (4)	3.7 (2)
Deaths	0	0	0	0	0	0
Serious adverse events	6.9 (2)	5.3 (3)	18.5 (5)	5.5 (3)	23.1 (6)	9.3 (5)
Serious adverse drug reactions	0	1.8 (1)	3.7 (1)	0	0	0
Adverse events leading to treatment discontinuation	3.4 (1)	5.3 (3)	3.7 (1)	0	3.8 (1)	0
Adverse events observed in ≥10% of subjects in any group						
Headache	10.3 (3)	10.5 (6)	7.4 (2)	10.9 (6)	0	3.7 (2)
Nausea	10.3 (3)	8.8 (5)	11.1 (3)	1.8 (1)	3.8 (1)	1.9 (1)
Diarrhoea	10.3 (3)	7.0 (4)	7.4 (2)	10.9 (6)	7.7 (2)	1.9 (1)
Pyrexia	0	5.3 (3)	0	10.9 (6)	11.5 (3)	16.7 (9)
COVID-19	0	3.5 (2)	3.7 (1)	1.8 (1)	34.6 (9)	20.4 (11)
Contusion	10.3 (3)	3.5 (2)	3.7 (1)	1.8 (1)	0	3.7 (2)
AST increased	10.3 (3)	3.5 (2)	3.7 (1)	1.8 (1)	0	0
Constipation	3.4 (1)	3.5 (2)	3.7 (1)	1.8 (1)	11.5 (3)	0
Anaemia	13.8 (4)	1.8 (1)	0	5.5 (3)	3.8 (1)	1.9 (1)
Insomnia	10.3 (3)	1.8 (1)	0	1.8 (1)	7.7 (2)	1.9 (1)
Asthenia	13.8 (4)	0	7.4 (2)	3.6 (2)	11.5 (3)	3.7 (2)

MedDRA/J ver. 25.1, incidence % (n)
In all parts, ravulizumab or eculizumab was coadministered.

No deaths occurred by the data cut-off date throughout the double-blind, continued treatment, and extension periods.

Serious adverse events were observed in the following subjects:
The double-blind period: 6.9% (2 of 29) of subjects in the placebo group (headache, anaemia, and abdominal pain in 1 subject each [1 subject developed ≥1 event]) and 5.3% (3 of 57) of subjects in the danicopan group (cholelithiasis, cholecystitis, blood bilirubin increased, pancreatitis, and COVID-19 in 1 subject each [some subjects developed ≥1 event])
The continued treatment period: 18.5% (5 of 27) of subjects in the placebo/danicopan group (haemolysis in 2 subjects, and vertigo, femur fracture, and headache in 1 subject each) and 5.5% (3 of 55) of subjects in the continued danicopan group (pyrexia, Dieulafoy's vascular malformation, COVID-19 pneumonia, and staphylococcal sepsis in 1 subject each [some subjects developed ≥1 event])
The extension period: 23.1% (6 of 26) of subjects in the placebo/danicopan group (COVID-19 in 2 subjects, and diarrhoea, body temperature increased, arthralgia, abdominal pain upper, haemorrhagic diathesis, neutropenic sepsis, disease progression, pericardial effusion, pneumonia, and cystitis in 1 subject each [some subjects developed ≥1 event]) and 9.3% (5 of 54) of subjects in the continued danicopan group (invasive ductal breast carcinoma, pulmonary haemorrhage, pulmonary embolism, Hb decreased, pyrexia, COVID-19, and stent-graft endoleak in 1 subject each [some subjects developed ≥1 event])

Of these events, blood bilirubin increased, pancreatitis, and headache in 1 subject each were serious adverse drug reactions, but all of these events resolved.

Adverse events leading to treatment discontinuation were observed in the following subjects:

The double-blind period: 3.4% (1 of 29) of subjects in the placebo group (AST increased) and 5.3% (3 of 57) of subjects in the danicopan group (hepatic enzyme increased, ALT increased, AST increased, blood bilirubin increased, and pancreatitis in 1 subject each [some subjects developed ≥1 event])
The continued treatment period: 3.7% (1 of 27) of subjects in the placebo/danicopan group (cholecystitis)
The extension period: 3.8% (1 of 26) of subjects in the placebo/danicopan group (hepatic function abnormal)

Of these events, AST increased in 2 subjects, and hepatic enzyme increased, ALT increased, hepatic function abnormal, pancreatitis, and blood bilirubin increased in 1 subject each were adverse drug reactions that led to treatment discontinuation. All of these adverse drug reactions resolved, except for hepatic enzyme increased (not resolved), AST increased (resolving, 1 subject) and hepatic function abnormal (resolving, 1 subject).

Meningococcal infection was not observed throughout the double-blind, continued treatment, and extension periods.

Safety in Japanese subjects:
The double-blind period (4 subjects in the placebo group and 8 subjects in the danicopan group):
Adverse events were observed in 25.0% (1 of 4) of subjects in the placebo group and 50.0% (4 of 8) of subjects in the danicopan group. Adverse drug reactions were observed in 0% of subjects in the placebo group and 25.0% (2 of 8) of subjects in the danicopan group (hypertension and hepatic function abnormal in 1 subject each). No adverse events were observed in ≥2 subjects in either group.
The continued treatment period (4 subjects in the placebo/danicopan group and 8 subjects in the continued danicopan group):
Adverse events were observed in 75.0% (3 of 4) of subjects in the placebo/danicopan group and 62.5% (5 of 8) of subjects in the continued danicopan group. Adverse drug reactions were observed in 25.0% (1 of 4) of subjects in the placebo/danicopan group (hepatic function abnormal) and 0% of subjects in the continued danicopan group. No adverse events were observed in ≥2 subjects in the placebo/danicopan group, but pyrexia was observed in 2 subjects in the continued danicopan group.
The extension period:
Adverse events were observed in 75.0% (3 of 4) of subjects in the placebo/danicopan group and 75.0% (6 of 8) of subjects in the continued danicopan group. Adverse drug reactions were observed in 25.0% (1 of 4) of subjects in the placebo/danicopan group (hepatic function abnormal) and 0% of subjects in the continued danicopan group. No adverse events were observed in ≥2 subjects in the placebo/danicopan group, but breakthrough haemolysis and pyrexia were observed in 2 subjects each in the continued danicopan group.

Adverse events and adverse drug reactions in Japanese subjects:
In the double-blind period, no serious adverse events were observed in either group. In the continued treatment period, 1 serious adverse event (femur fracture) was observed in 1 subject in the placebo/danicopan group, but no serious adverse events were observed in the continued danicopan group. In the extension period, serious adverse events were observed in the placebo/danicopan group (disease progression, pneumonia, and cystitis in 1 subject each), but no serious adverse events were observed in the continued danicopan group. All of these

events resolved. There were no serious adverse drug reactions. Adverse events leading to treatment discontinuation were hepatic function abnormal in 1 subject in the placebo/danicopan group in the extension period, but none were observed in the continued danicopan group. The hepatic function abnormal was an adverse drug reaction, but it was resolving.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

On the basis of the investigations in Sections 7.R.1.1 to 7.R.1.3, PMDA considers that danicopan was shown to have efficacy in patients with PNH with an inadequate response to complement C5 inhibitors, and is expected to have clinically meaningful efficacy in Japanese patients.

7.R.1.1 Plan and main results of the global phase III study (Study 301)

The applicant's explanation about the appropriateness of the plan of the confirmatory Study 301 and the main study results:

The objective of Study 301 was to evaluate the efficacy and safety of danicopan in patients with PNH presenting with anemia even under treatment with a complement C5 inhibitor, the standard-of-care treatment for PNH. The study population was therefore defined as patients already receiving ravulizumab or eculizumab (complement C5 inhibitors that had been approved when the study was planned) who have anemia with an absolute reticulocyte count of $\geq 120 \times 10^9$/L plus an Hb level of ≤9.5 g/dL. In view of a report that showed a positive correlation between the Hb level and the quality of life (QOL) of patients with anemia associated with chronic kidney disease (*Curr Med Res Opin*. 2006;22:1929-1937), the primary endpoint was defined as the change in Hb level from baseline to Week 12. When the study was planned, there were no treatment drugs confirmed to be effective in patients with PNH with an inadequate response to complement C5 inhibitors; therefore, the study was designed to demonstrate the superiority of danicopan over placebo.

Table 41 shows the results of the primary endpoint. The superiority of danicopan over placebo was demonstrated ($P < 0.0001$, MMRM, 2-sided significance level 0.018). The intergroup difference (least squares mean) was 2.44 g/dL, which was greater than the clinically meaningful difference of 2 g/dL.

In the Japanese subpopulation, the mean ± standard deviation of the "change in Hb level from baseline to Week 12" was −0.30 ± 0.28 g/dL in the placebo group (2 subjects) and 2.58 ± 1.64 g/dL in the danicopan group (5 subjects). These results were similar to those in the entire population (Table 43).

Table 43. Change in Hb level (g/dL) from baseline to Week 12
(Double-blind period: Interim Efficacy Analysis Set)

	Entire population		Japanese subpopulation	
	Placebo	Danicopan	Placebo	Danicopan
Hb level at baseline	7.74 ± 1.04 (21)	7.66 ± 0.94 (42)	7.70 ± 0.42 (2)	6.96 ± 1.13 (5)
Change in Hb level from baseline to Week 12	0.65 ± 0.91 (20)	3.15 ± 1.27 (36)	−0.30 ± 0.28 (2)	2.58 ± 1.64 (5)

Mean ± standard deviation (No. of subjects evaluated)

As for changes from baseline in Hb level in the double-blind period, the danicopan group showed an increased Hb level at Week 2, which was maintained until Week 12 (Figure 1).

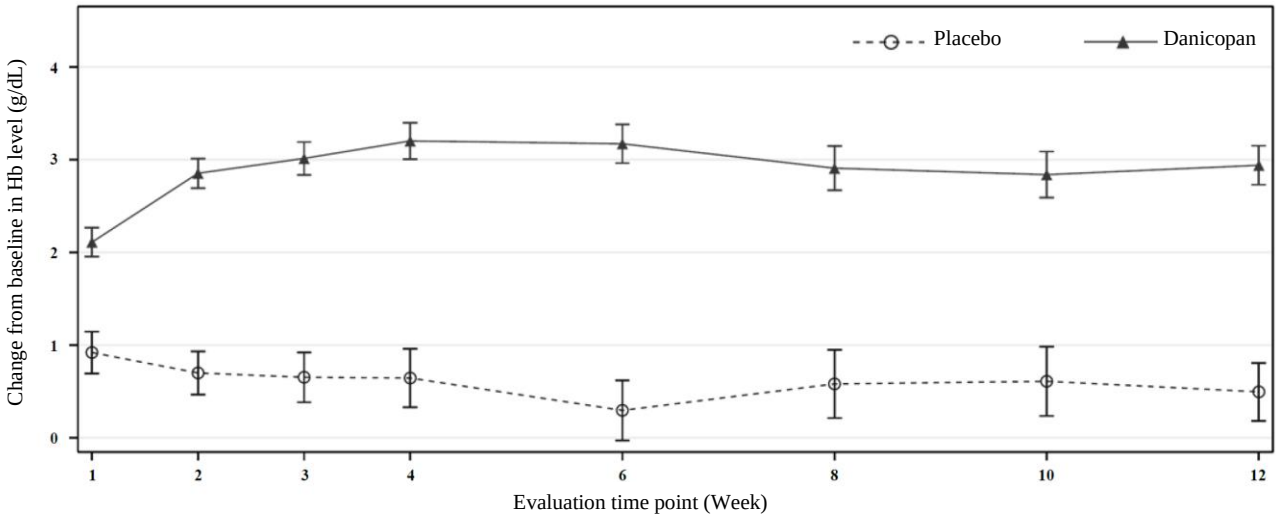


Figure 1. Changes from baseline in Hb level
(Least squares mean ± standard deviation) (double-blind period: Interim Efficacy Analysis Set)

The percentage of subjects with an increase of ≥2 g/dL in Hb level at Week 12 without blood transfusion tended to be higher in the danicopan group: 0% (0 of 21) of subjects in the placebo group and 59.5% (25 of 42) of subjects in the danicopan group. In the Japanese subpopulation, the percentage was 0% (0 of 2) of subjects in the placebo group and 60.0% (3 of 5) of subjects in the danicopan group. These results were similar to those in the entire population (Table 44).

Table 44. Percentage of subjects with a ≥2 g/dL increase in Hb level at Week 12 without blood transfusion
(Double-blind period: Interim Efficacy Analysis Set)

	Entire population			Japanese subpopulation	
	Placebo (21 subjects)	Danicopan (42 subjects)	Intergroup difference (danicopan – placebo)	Placebo (2 subjects)	Danicopan (5 subjects)
Percentage % (No. of subjects)	0	59.5 (25)	46.9	0	60.0 (3)
[95% CI]	[0.0, 16.1]	[43.3, 74.4]	[29.2, 64.7]	[0.0, 84.2]	[14.7, 94.7]

The percentage of subjects without blood transfusion for 12 weeks from the start of treatment[52)] tended to be higher in the danicopan group: 38.1% (8 of 21 of subjects) in the placebo group and 83.3% (35 of 42 of subjects) in the danicopan group. In the Japanese subpopulation, the percentage was 50.0% (1 of 2 of subjects) in the placebo group and 100% (5 of 5 of subjects) in the danicopan group. These results were similar to those in the entire population (Table 45).

[52)] The "percentage of subjects without blood transfusion for 12 weeks from the start of treatment" in this study was defined as the "percentage of subjects who did not require protocol-specified blood transfusion between the start of study treatment and Week 12." Subjects who discontinued the study treatment before Week 12 were regarded as not having achieved this endpoint.

Table 45. Percentage of subjects without blood transfusion for 12 weeks from the start of treatment (Double-blind period: Interim Efficacy Analysis Set)

	Entire population			Japanese subpopulation	
	Placebo (21 subjects)	Danicopan (42 subjects)	Intergroup difference (danicopan – placebo)	Placebo (2 subjects)	Danicopan (5 subjects)
Percentage % (No. of subjects)	38.1 (8)	83.3 (35)	41.7	50.0 (1)	100 (5)
[95% CI]	[18.1, 61.6]	[68.6, 93.0]	[22.7, 60.8]	[1.3, 98.7]	[47.8, 100]

On the basis of the results of the primary endpoint and secondary endpoints in Study 301, as presented above, PMDA considers that the efficacy of danicopan has been demonstrated in patients with PNH with an inadequate response to the complement C5 inhibitor ravulizumab or eculizumab.

PMDA's view:

The objective of Study 301 is to confirm the improvement of anemia by add-on danicopan in patients with PNH who have anemia even under treatment with a complement C5 inhibitor; the target population, primary endpoint, comparator, etc. set for the study were appropriate. Study 301 demonstrated the superiority of danicopan over placebo in terms of the change in Hb level from baseline to Week 12, the primary endpoint. The percentage of subjects with an increase of ≥2 g/dL in Hb level at Week 12 without blood transfusion (secondary endpoint) and the percentage of subjects without blood transfusion for 12 weeks from the start of treatment (secondary endpoint) also tended to be higher in the danicopan group than in the placebo group. Based on these results of the primary and secondary endpoints, PMDA considers that danicopan was shown to have clinically meaningful efficacy. The results of both the primary and secondary endpoints in the Japanese subpopulation showed a similar trend to those in the entire population, although there are limitations to the evaluation due to the limited number of Japanese subjects studied. In view of the above, danicopan is expected to have meaningful efficacy in Japanese patients with PNH who have an inadequate response to complement C5 inhibitors.

7.R.1.2 Efficacy by patient characteristics

The applicant's explanation about the efficacy of danicopan by patient characteristics:

Table 46 shows the change in Hb level from baseline to Week 12 by major patient characteristics in Study 301 (data cut-off of [redacted], 20[redacted]). The change tended to be larger in the danicopan group than in the placebo group for all subgroups.

Table 46. Change in Hb level (g/dL) from baseline to Week 12 by patient characteristics (Double-blind period: Interim Efficacy Analysis Set)

		Placebo	Danicopan
Sex	Female	0.55 ± 0.76 (13)	3.17 ± 1.42 (18)
	Male	0.81 ± 1.20 (7)	3.13 ± 1.15 (18)
Age	<65 years	0.74 ± 0.95 (16)	3.09 ± 1.28 (27)
	≥65 years	0.25 ± 0.70 (4)	3.33 ± 1.32 (9)
Hb level at screening	<8.5 g/dL	0.67 ± 1.00 (13)	3.07 ± 1.32 (23)
	≥8.5 g/dL	0.60 ± 0.79 (7)	3.28 ± 1.22 (13)
Prior blood transfusion (No. of times during the 6 months before screening)	≤2 times	0.73 ± 1.11 (12)	3.24 ± 1.18 (19)
	≥3 times	0.51 ± 0.53 (8)	3.05 ± 1.40 (17)
Coadministered complement C5 inhibitor	Ravulizumab	1.02 ± 1.06 (10)	3.33 ± 1.38 (25)
	Eculizumab	0.27 ± 0.57 (10)	2.74 ± 0.91 (11)

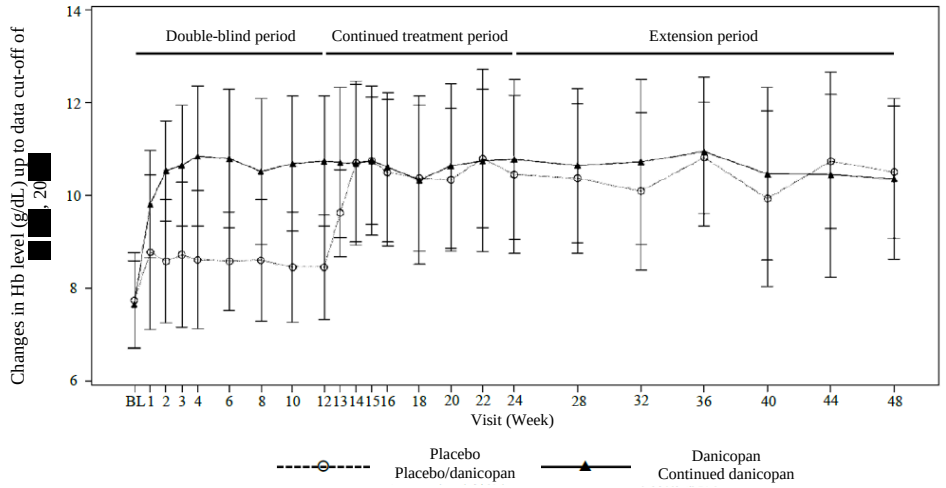
Mean ± standard deviation (No. of subjects)

Hb levels tended to be higher in the danicopan group than in the placebo group for all subgroups, although there are limitations to the evaluation due to the limited number of subjects in some subgroups. PMDA therefore considers that the values or changes of these patient characteristics are unlikely to significantly affect the efficacy of danicopan.

7.R.1.3 Long-term efficacy

The applicant's explanation about the long-term efficacy of danicopan:

Figure 2 shows changes in Hb level up to Week 48 in Study 301. The continued danicopan group showed an improved Hb level at Week 12, which was maintained until Week 48. The placebo/danicopan group also showed increased Hb levels after Week 12 (when placebo was switched to danicopan), which were maintained until Week 48.



No. of subjects evaluated in the danicopan (continued danicopan) group	42	38	41	35	40	38	35	26	36	31	35	33	29	30	31	35	32	30	24	22	20	16
No. of subjects evaluated in the placebo (placebo/danicopan) group	21	19	19	18	20	20	20	18	20	17	18	17	20	17	16	16	16	13	13	11	9	10

Figure 2. Changes in Hb level
(Mean ± standard deviation; Interim Efficacy Analysis Set)

On the basis of the results of Study 301, PMDA considers that the efficacy of danicopan is expected to be maintained during long-term treatment.

7.R.2 Safety

PMDA's view:

On the basis of the investigations in Sections 7.R.2.1 to 7.R.2.3, PMDA considers that the safety of danicopan can be controlled if it is used by a suitable physician at a suitable medical institution (i.e., both of which should be familiar with the diagnosis and treatment of PNH and be fully capable of managing the risks, etc. associated with danicopan), in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection. Since the number of Japanese subjects evaluated in Study 301 is limited, the safety data of danicopan in Japanese patients with PNH should be collected and evaluated through post-marketing surveillance.

7.R.2.1 Incidence of adverse events in Study 301

The applicant's explanation about the incidence of adverse events in Study 301:

Table 42 shows the incidence of adverse events in the double-blind period of Study 301. There were no major differences in the incidence of adverse events between the placebo and danicopan groups. After the data cut-off of March 31, 2023, 1 subject[53)] in the placebo/danicopan group died (pneumonia) but the death was unrelated to the study drug, and the subject did not have meningococcal infection. As for the incidence of adverse events in the Japanese subpopulation, no adverse events occurred in ≥2 subjects and no Japanese-specific safety concerns were identified, although there are limitations to the interpretation of study results due to the limited number of Japanese subjects [see Section 7.2.1].

Table 47 shows the incidence of adverse events by time of onset in the population of subjects who received danicopan in Study 301. The incidence of adverse events did not increase over time.

Table 47. Incidence of adverse events by time of onset (Study 301, safety analysis population, data cut-off of March 31, 2023)

	Time to onset from the start of danicopan treatment					
	Weeks 0 to 12 (N = 84)	Weeks 12 to 24 (N = 81)	Weeks 24 to 36 (N = 79)	Weeks 36 to 52 (N = 69)	After Week 52 (N = 51)	Entire period (N = 84)
All adverse events	72.6 (61)	71.6 (58)	45.6 (36)	50.7 (35)	64.7 (33)	95.2 (80)
All adverse drug reactions	22.6 (19)	6.2 (5)	5.1 (4)	1.4 (1)	2.0 (1)	25.0 (21)
Serious adverse events	9.5 (8)	6.2 (5)	1.3 (1)	7.2 (5)	7.8 (4)	20.2 (17)
Serious adverse drug reactions	2.4 (2)	0	0	0	0	2.4 (2)
Adverse events leading to treatment discontinuation	4.8 (4)	1.2 (1)	0	0	0	6.0 (5)
Adverse drug reactions leading to treatment discontinuation	3.6 (3)	1.2 (1)	0	0	0	4.8 (4)
Adverse events observed in ≥10% of subjects in the entire period						
COVID-19	3.6 (3)	2.5 (2)	10.1 (8)	5.8 (4)	13.7 (7)	28.6 (24)
Pyrexia	3.6 (3)	9.9 (8)	2.5 (2)	5.8 (4)	11.8 (6)	22.6 (19)
Headache	9.5 (8)	7.4 (6)	2.5 (2)	0	0	15.5 (13)
Diarrhoea	7.1 (6)	9.9 (8)	0	1.4 (1)	3.9 (2)	14.3 (12)
Nausea	9.5 (8)	2.5 (2)	0	2.9 (2)	0	11.9 (10)
Arthralgia	6.0 (5)	1.2 (1)	0	4.3 (3)	3.9 (2)	10.7 (9)
Fatigue	3.6 (3)	3.7 (3)	2.5 (2)	1.4 (1)	2.0 (1)	10.7 (9)
Adverse drug reactions observed in ≥3 subjects in the entire period						
Nausea	6.0 (5)	0	0	0	0	6.0 (5)
Headache	3.6 (3)	0	0	0	0	3.6 (3)
Hepatic function abnormal	2.4 (2)	1.2 (1)	0	0	0	3.6 (3)
Pyrexia	2.4 (2)	2.5 (2)	0	0	0	3.6 (3)

MedDRA/J ver. 25.1, incidence % (n)

PMDA has concluded that there are no particular safety concerns about the safety of danicopan, in view of the applicant's explanation about (a) the incidence of adverse events in the placebo and danicopan groups in the double-blind period (12 weeks) of Study 301, (b) safety concerns specific to the Japanese population, and (c) the trend in the incidence of adverse events during long-term treatment with danicopan. Adverse events of special interest are described in detail in Section 7.R.2.2.

53) A [redacted]-year-old Japanese man. He received concomitant ravulizumab. Treatment was started with danicopan 150 mg TID in the continued treatment period, which was increased to 200 mg TID from Week 18. He developed pneumonia on Study Day 325 and died on Study Day 347.

7.R.2.2 Adverse events of special interest

PMDA has come to the following conclusions about meningococcal infection and hepatic enzyme increased, which are specified as adverse events of special interest.

7.R.2.2.1 Meningococcal infection

The applicant's explanation about meningococcal infection:

Danicopan potently and selectively inhibits the functions of complement D factor, thereby preventing activation of the alternative complement pathway. Accordingly, danicopan inhibits part of the complement-mediated infection-fighting mechanism and as a result may increase susceptibility to meningococcal infection. Meningococcal infection is therefore an important potential risk of danicopan. Complement C5 inhibitors, which must in principle be coadministered with danicopan, also have a risk of meningococcal infection. For these reasons, meningococcal infection[54)] was classified as an adverse event of special interest.

In view of the risk of meningococcal infection due to the effect of danicopan, "Having received or will receive meningococcal vaccination" was specified as an inclusion criterion of the foreign phase II study (Study ACH471-101) and Study 301; meningococcal infection did not occur in these 2 studies. Among the completed or ongoing clinical studies of danicopan[55)] as of [redacted], 20[redacted], the phase I studies had no vaccination-related eligibility criteria, but the other studies had such criteria. None of these studies have reported the occurrence of meningococcal infection. Further, danicopan does not inhibit any components specific to the classical complement pathway, lectin complement pathway, or terminal complement pathway. This suggests that danicopan, when coadministered with complement C5 inhibitors, will not increase the risk of meningococcal infection associated with complement C5 inhibitor monotherapy. In view of the above, the following precautionary statements regarding the risk of meningococcal infection associated with danicopan should be provided in the package insert:

(a) Danicopan should be used only by a suitable physician at a suitable medical institution (i.e., both of which should be familiar with the diagnosis and treatment of PNH and be fully capable of managing the risks, etc. associated with danicopan), in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

(b) The patient should be confirmed to have received meningococcal vaccination before the start of danicopan treatment.

In Study 301, subjects were not required to receive vaccination against *Pneumococcus* or *Haemophilus influenzae*, which are also encapsulated bacteria, but 2 of 86 subjects had received vaccines against either of

54) Events classified as MedDRA PT "meningococcal bacteraemia," "meningitis meningococcal," "meningococcal infection," "meningococcal sepsis," "meningococcal carditis," "encephalitis meningococcal," "endocarditis meningococcal," "myocarditis meningococcal," "optic neuritis meningococcal," or "pericarditis meningococcal."

55) The following studies of danicopan: Phase I studies (Studies ACH471-001, ACH471-002, ACH471-005, ACH471-006, ACH471-009, ACH471-010, ACH471-011, ACH471-012, ACH471-013, ACH471-014, ACH471-016, ACH471-017, ALXN2040-HV-101, ALXN2040-HV-102, and ALXN2040-HV-119); phase II studies in patients with PNH (Studies ACH471-100, ACH471-101, and ACH471-103); phase III studies in patients with PNH (Studies 301 and ALXN2040-PNH-303); phase II studies in patients with complement 3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis (Studies ACH471-201, ACH471-204, and ACH471-205); and a phase II study in patients with geographic atrophy (Study ALXN2040-GA-201).

these bacteria. Adverse events related to encapsulated bacterial infections (*Pneumococcus* and *Haemophilus influenzae*) did not occur in Study 301. In the completed or ongoing clinical studies of danicopan that did not require subjects to receive vaccination[56] (as of [redacted], 20[redacted]), encapsulated bacterial infections other than meningococcal infection[57] have not occurred. Danicopan does not inhibit any components specific to the classical complement pathway, lectin complement pathway, or terminal complement pathway and allows maintenance of immune functions of the classical and lectin complement pathways against infections; this suggests that the immune functions against *Pneumococcus* and *Haemophilus influenzae* can be maintained even when danicopan is administered. Further, a review article summarizing the risks of infections in patients deficient in complement components (*Clin Microbiol Rev*. 1991;4:359-395) states that the main risk of infections in patients with factor D deficiency is meningococcal infection. In view of these findings, the applicant considers it unnecessary to provide any particular precautions regarding the risk of other encapsulated bacterial infections (*Pneumococcus* and *Haemophilus influenzae*) or to require patients to receive vaccination against *Pneumococcus* or *Haemophilus influenzae* before receiving danicopan.

PMDA's view:

In view of the mechanism of action of danicopan, there is a concern about the risk of meningococcal infection during danicopan treatment, although meningococcal infection has not occurred in clinical studies (as of the data cut-off on March 31, 2023). Danicopan should therefore be used only by a suitable physician at a suitable medical institution (i.e., both of which should be familiar with the diagnosis and treatment of PNH and be fully capable of managing the risks, etc. associated with danicopan), in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection. Since it is also important to take appropriate measures against meningococcal infection when administering danicopan, precautions should be provided in the package insert, materials for healthcare professionals, and/or materials for patients, to thoroughly ensure the following:

(a) Patients should be checked for their prior vaccination against *Meningococcus* before receiving danicopan.
(b) A meningococcal vaccine should be administered to patients who have never received the vaccination or require additional vaccination.

In view of the applicant's explanation about the mechanism of action of danicopan and the status of vaccination in Study 301, the applicant's explanation that vaccination against *Pneumococcus* and *Haemophilus influenzae* (i.e., encapsulated bacteria other than *Meningococcus*) is not required before the start of danicopan treatment, is appropriate. However, since inhibition of the complement pathway by danicopan may pose a certain risk of infection, precautions regarding the increased risk of infection should be provided in the package insert.

[56] The following studies of danicopan: Phase I studies (Studies ACH471-001, ACH471-002, ACH471-005, ACH471-006, ACH471-009, ACH471-010, ACH471-011, ACH471-012, ACH471-013, ACH471-014, ACH471-016, ACH471-017, ALXN2040-HV-101, ALXN2040-HV-102, and ALXN2040-HV-119); phase III studies in patients with PNH (Studies 301 and ALXN2040-PNH-303); and a phase II study in patients with geographic atrophy (Study ALXN2040-GA-201).

[57] Events classified as MedDRA HLT "Haemophilus infections," or PT "pneumonia streptococcal" or "Haemophilus influenzae type b immunisation," or events that include the PT term "pneumococcal."

7.R.2.2.2 Hepatic enzyme increased

The applicant's explanation about hepatic enzyme increased:

In Study ACH471-002 in non-Japanese healthy adults [see Section 6.2.3], ALT increased and AST increased developed after completion of danicopan treatment in 2 subjects who received danicopan 500 mg BID or 800 mg BID. Hepatic enzyme increased[58)] was therefore classified as an adverse event of special interest.

As of the data cut-off of March 31, 2023 in Study 301, hepatic enzyme increased was observed in 10.3% (3 of 29) of subjects in the placebo group and 14.0% (8 of 57) of subjects in the danicopan group in the double-blind period; 11.1% (3 of 27) of subjects in the placebo/danicopan group and 5.5% (3 of 55) of subjects in the continued danicopan group in the continued treatment period; and 3.8% (1 of 26) of subjects in the placebo/danicopan group and 1.9% (1 of 54) of subjects in the continued danicopan group in the extension period (Table 48). The percentage of subjects with ALT >3 × ULN in the double-blind period was 3.4% (1 of 29) of subjects in the placebo group and 14.0% (8 of 57) of subjects in the danicopan group. Of the 8 subjects with ALT >3 × ULN in the danicopan group, 5 had ALT >3 to ≤5 × ULN, 1 had ALT >5 to ≤8 × ULN, and 2 had ALT >8 × ULN. In view of the above, precautions will be provided in the package insert to ensure that hepatic function tests are performed on a regular basis before the start of, as well as during, danicopan treatment.

Table 48. Breakdown of hepatic enzyme increased by treatment period in Study 301(data cut-off of March 31, 2023)

	Double-blind period		Continued treatment period		Extension period	
	Placebo (N = 29)	Danicopan (N = 57)	Placebo/danicopan (N = 27)	Continued danicopan (N = 55)	Placebo/danicopan (N = 26)	Continued danicopan (N = 54)
Total of hepatic enzyme increased	10.3 (3)	14.0 (8)	11.1 (3)	5.5 (3)	3.8 (1)	1.9 (1)
Breakdown of hepatic enzyme increased						
ALT increased	3.4 (1)	5.3 (3)	0	0	0	0
AST increased	10.3 (3)	3.5 (2)	3.7 (1)	1.8 (1)	0	0
Blood bilirubin increased	0	3.5 (2)	0	1.8 (1)	0	1.9 (1)
Hepatic function abnormal	0	1.8 (1)	3.7 (1)	0	3.8 (1)	0
Liver disorder	0	1.8 (1)	0	0	0	0
Hepatic enzyme increased	0	1.8 (1)	0	0	0	0
Transaminases increased	0	0	0	1.8 (1)	0	0
Portal vein dilatation	0	0	0	1.8 (1)	0	0
Hyperbilirubinaemia	0	0	3.7 (1)	0	0	0

MedDRA/J ver. 25.1, incidence % (n)

PMDA's view:

ALT increased and AST increased were observed in Study ACH471-002 in healthy adults, and hepatic enzyme increased and ALT increased were observed in Study 301. Therefore the applicant's plan (i.e., to provide precautions in the package insert to ensure that hepatic function tests are performed on a regular basis before the start of, as well as during, danicopan treatment) is appropriate.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of danicopan:

[58)] Events classified as MedDRA SMQ "Drug related hepatic disorders - severe events only (narrow)" or "Liver related investigations, signs and symptoms (narrow)."

PNH is a disease characterized by hemolysis due to uncontrolled complement activation. The current standard-of-care treatment for PNH is complement C5 inhibitors. Complement C5 inhibitors improve intravascular hemolysis but cannot be expected to be effective for extravascular hemolysis caused by opsonization of C3b, upstream of C5. As a drug for the treatment of PNH with an inadequate response to complement C5 inhibitors, the complement C3 inhibitor pegcetacoplan has been approved and is used in patients switched from complement C5 inhibitors. However, since pegcetacoplan monotherapy only inhibits upstream of the complement pathway, there is concern that inadequate inhibition of complement C3 may lead to amplification of the downstream cascade and result in more serious breakthrough hemolysis (*N Engl J Med*. 2022;387:160-166). The risk of infection with other encapsulated bacteria (*Pneumococcus* and *Haemophilus influenzae*) besides *Meningococcus* is another concern.

Danicopan is expected to inhibit extravascular hemolysis by inhibiting complement factor D, which is involved in complement C3 activity. Since danicopan is used as an add-on to complement C5 inhibitors, patients using danicopan can achieve inhibition of both upstream and downstream of the complement C5 pathway, with a low risk of infection with encapsulated bacteria (i.e., *Pneumococcus* and *Haemophilus influenzae*) other than *Meningococcus*. The superiority of danicopan over placebo was demonstrated [see Section 7.R.1] with no major safety concerns [see Section 7.R.2] in Study 301, which investigated the efficacy and safety of danicopan in combination with the complement C5 inhibitor ravulizumab or eculizumab in patients with PNH with an inadequate response to ravulizumab or eculizumab. Danicopan is therefore considered to be a new treatment option for patients with PNH with an inadequate response to ravulizumab or eculizumab.

PMDA's view:
The superiority of danicopan over placebo was demonstrated in Study 301 in patients with PNH with an inadequate response to complement C5 inhibitors [see Section 7.R.1], and the safety of danicopan is considered to be controllable if it is administered under the supervision of a physician who has adequate knowledge of PNH and is familiar with the risks associated with danicopan [see Section 7.R.2]. Taking the efficacy obtained with danicopan into account, its safety is clinically acceptable. Danicopan is therefore considered to be a new treatment option for patients with PNH with an inadequate response to complement C5 inhibitors.

7.R.4 Indication

The applicant's explanation about the indication of danicopan:
Study 301 investigated the efficacy and safety of danicopan as add-on therapy to the complement C5 inhibitor ravulizumab or eculizumab in patients with PNH with an inadequate response to ravulizumab or eculizumab. In the study, the superiority of danicopan over placebo was demonstrated, and the results in the Japanese subpopulation showed a similar trend to those in the entire population [see Section 7.R.1]. No major concerns about the safety of danicopan were identified [see Section 7.R.2]. Since danicopan is considered to be effective for extravascular hemolysis that cannot be controlled by inhibiting the terminal complement pathway of complement C5, (a) the indication of danicopan should be "inhibition of extravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria" and (b) the "Precautions Concerning Indication" section in the

package insert should include a statement to the effect that danicopan should be administered to patients with extravascular hemolysis under treatment with ravulizumab or eculizumab.

PMDA's view:
Study 301 in patients with PNH with an inadequate response to the complement C5 inhibitor ravulizumab or eculizumab demonstrated the superiority of danicopan over placebo and suggested the effectiveness of danicopan in the Japanese population as well [see Section 7.R.1]. No major safety concerns were identified in the danicopan group, compared with the placebo group, and the safety of danicopan is controllable if it is administered under the supervision of a physician who has adequate knowledge of PNH and is familiar with the risks associated with danicopan [see Section 7.R.2]. The applicant has proposed "inhibition of extravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria" for the indication of danicopan and plans to include a precautionary statement (i.e., danicopan should be administered to patients with extravascular hemolysis under treatment with ravulizumab or eculizumab) under "Precautions Concerning Indication" in the package insert.

However, the study population of Study 301 is patients with PNH who have anemia (Hb ≤9.5 g/dL) with an inadequate response to a complement C5 inhibitor, not limited to those with extravascular hemolysis. In addition, the primary endpoint of Study 301 is the "change in Hb level from baseline to Week 12," which is not an endpoint intended for the effect on extravascular hemolysis alone. Since no standardized method for diagnosing and evaluating "extravascular hemolysis" has been established in clinical practice, the term "extravascular hemolysis" should not be used in the indication. Further, the specific drug names "ravulizumab or eculizumab" included in the statement under "Precautions Concerning Indication" should be replaced by a more general term such as "complement C5 inhibitors," which represents their mechanism of action.

In view of the above, the indication of danicopan should be "paroxysmal nocturnal hemoglobinuria" and "Precautions Concerning Indication" should include the following statement: "Danicopan should be administered in combination with a complement C5 inhibitor to patients with an inadequate response to appropriate treatment with a complement C5 inhibitor."

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration of danicopan

The applicant's explanation about the dosage and administration of danicopan:
In Study 301, the starting dose of danicopan defined at the start of study was 150 mg TID basically but 100 mg TID for patients with ALT or direct bilirubin >1.5 × ULN at screening. However, on the basis of the results of several foreign phase II studies in patients with PNH or patients with complement 3 glomerulopathy or immune-complex membranoproliferative glomerulonephritis (IC-MPGN) (Studies ACH471-101, ACH471-103, ACH471-204, and ACH471-205), the starting dose of 100 mg TID was abolished during the study and therefore 150 mg TID became the only choice.[48)] A dose increase to up to 200 mg TID at the investigator's discretion was allowed in patients with an inadequate response. Only 3 subjects had started danicopan treatment at 100 mg TID before the starting dose was abolished. As of the data cut-off of [redacted], 20[redacted], 68.8% (55 of 80)

of subjects underwent a dose increase to 200 mg TID. In 19.0% (8 of 42) of subjects, Hb level at 2 weeks after a dose increase was ≥1.0 g/dL higher than that before a dose increase.

As for safety, both 150 mg TID and 200 mg TID were well-tolerated, with no difference in the incidence of adverse events between the doses (Table 49).

Table 49. Incidence of adverse events by dose (Studies 101 and 301)

	100 mg TID (N = 13)	150 mg TID (N = 91)	200 mg TID (N = 63)	Total (N = 92)
Mean duration of treatment	189.2 days	149.7 days	298.3 days	379.1 days
All adverse events	92.3 (12)	74.7 (68)	81.0 (51)	91.3 (84)
All adverse drug reactions	30.8 (4)	22.0 (20)	7.9 (5)	26.1 (24)
Serious adverse events	15.4 (2)	9.9 (9)	19.0 (12)	22.8 (21)
Serious adverse drug reactions	7.7 (1)	2.2 (2)	0	3.3 (3)
Adverse events leading to discontinuation	7.7 (1)	3.3 (3)	1.6 (1)	5.4 (5)
Adverse drug reactions leading to discontinuation	0	3.3 (3)	1.6 (1)	4.3 (4)
Hepatic enzyme increased	30.8 (4)	14.3 (13)	7.9 (5)	21.7 (20)
Meningococcal infection	0	0	0	0

Incidence % (n)

In view of the above, the applicant considers that the usual dosage and administration of danicopan should be 150 mg TID orally in combination with ravulizumab or eculizumab, and that a dose increase to 200 mg TID should be allowed in patients with an inadequate response.

PMDA's view:

Study 301 demonstrated the efficacy of danicopan as an add-on to a complement C5 inhibitor [see Section 7.R.1], and the safety of danicopan is controllable if it is administered under the supervision of a physician who has adequate knowledge of PNH and is familiar with the risks associated with danicopan [see Section 7.R.2]. In Study 301, all subjects excluding 3 in the danicopan group started treatment at 150 mg TID. The dose was increased to 200 mg TID in approximately 70% of subjects, and Hb levels increased by ≥1.0 g/dL after the dose increase in approximately 20% of subjects. A pooled analysis of Studies 101 and 301 showed no differences in safety between the doses. In view of the above, it is reasonable to (a) set "danicopan 150 mg TID orally" (i.e., the dosage regimen in Study 301) as the usual dosage and administration and (b) allow a dose increase to 200 mg TID in patients with an inadequate response.

7.R.5.2 Actions to be taken when discontinuing danicopan treatment

The applicant's explanation about actions to be taken when discontinuing danicopan treatment:

In Study ACH471-002 in non-Japanese healthy adults [see Section 6.2.3], 2 subjects receiving danicopan 500 or 800 mg BID experienced ALT increased and AST increased after discontinuing the treatment without tapering its dose. Study 301 therefore required that danicopan dose be tapered over 6 days (100 mg TID for 3 days, followed by 50 mg TID for 3 days) before discontinuing the treatment. This discontinuation method showed favorable safety in Study 301. Therefore the following precautionary statements should be disseminated: "If danicopan treatment is discontinued, taper the dose over at least 6 days (100 mg TID for 3 days, followed by 50 mg TID for 3 days) before discontinuation" (as in Study 301) and "Hemolysis and

accompanying clinical symptoms should be carefully monitored while tapering the dose and appropriate actions should be taken as needed."

PMDA's view:

There was a safety concern about discontinuation of danicopan after high-dose treatment, and the method of discontinuing danicopan used in Study 301 (i.e., dose tapering before discontinuation) showed no major safety concerns. In view of this, the package insert should include a precautionary statement to the effect that danicopan dose should be tapered over at least 6 days before discontinuing the treatment, as in Study 301. In addition, since there is a risk of hemolysis during dose tapering, the package insert should also include a precautionary statement to the effect that hemolysis and accompanying clinical symptoms should be carefully monitored and appropriate actions should be taken as needed.

7.R.6 Post-marketing investigation

The applicant plans to conduct a general use-results survey covering all patients treated with danicopan after the market launch, as shown in Table 50.

Table 50. Outline of general use-results survey (draft)

Objective	To collect the safety and efficacy data of danicopan.
Survey method	All-case surveillance
Planned sample size	50 patients
Survey period	Date of approval to 7 years after approval
Registration period	Date of approval to 5 years after approval or the time point when 50 patients have been registered, whichever comes first
Observation period	24 weeks
Main survey items	• Patient characteristics: Age, sex, reason for use of danicopan, history of meningococcal infection, date of PNH diagnosis, findings of extravascular hemolysis, prior participation in clinical studies of danicopan, medical history, concurrent illness, etc. • Status of vaccination: Prior vaccination (meningococcal vaccine, pneumococcal vaccine, Hib vaccine) • Prior treatment for PNH: Blood transfusion (date of transfusion, number of transfusions, number of units) and other concomitant treatments • Status of danicopan treatment: Date of administration, dosage regimen (if changed or discontinued, the reason) • Efficacy: Change in LDH, change in Hb level, change in QOL, change in the number of units of blood transfusion • Laboratory tests: AST, ALT, LDH, bilirubin, etc. • Adverse events: Date of onset, seriousness, outcome, discontinuation of danicopan (yes/no), causal relationship to danicopan, etc.

PMDA's view:

The safety of danicopan has not been fully investigated because only a limited number of Japanese patients with PNH received danicopan in Study 301. Therefore the applicant should conduct a post-marketing survey covering all treated patients. Details of the survey plan, including the observation period, should be further examined.

8. Results of Compliance Assessment Concerning the New Drug Application Data and the 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 document-based inspection and 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 5.3.5.1-1) were subjected to 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 danicopan has efficacy in the treatment of paroxysmal nocturnal hemoglobinuria and acceptable safety in view of its benefits. Danicopan is clinically meaningful because it offers a new treatment option for patients with paroxysmal nocturnal hemoglobinuria.

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

Review Report (2)

November 27, 2023

Product Submitted for Approval

Brand Name	Voydeya Tablets 50 mg
Non-proprietary Name	Danicopan
Applicant	Alexion Pharma GK
Date of Application	May 19, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

The comments made during the Expert Discussion and the subsequent review conducted by 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 the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

At the Expert Discussion, the expert advisors supported PMDA's conclusion described in Section "7.R.1 Efficacy" of the Review Report (1). In addition, the following comments on the efficacy of danicopan in Study 301 were raised by the expert advisors:

- Since Japanese subjects enrolled in Study 301 are extremely limited, the efficacy in the Japanese subpopulation of Study 301 should be confirmed using data obtained after the data cut-off ([redacted], 20[redacted]) of additional analysis [1] (additional analysis [1] was used for efficacy analysis).
- The population PK analysis suggested that body weight may affect the PK of danicopan [see Section 6.2.14 of the Review Report (1)]. Whether body weight affected the efficacy of danicopan in Study 301 should be confirmed.

The applicant's explanation about efficacy in all Japanese subjects enrolled in Study 301 and efficacy by body weight:

Table 51 shows efficacy results (i.e., the change in Hb level from baseline to Week 12) in the Japanese subpopulation of Study 301 based on the latest available data (data cut-off of March 31, 2023). These results did not tend to markedly differ from the results in the entire population in additional analysis [1] (Table 41). Danicopan is therefore expected to have efficacy in Japanese patients with PNH even based on the latest data.

Table 51. Change in Hb level (g/dL) from baseline to Week 12
(Double-blind period: data cut-off of March 31, 2023)

	Japanese subpopulation	
	Placebo	Danicopan
Hb level at baseline	8.20 ± 0.71 (4)	6.84 ± 1.04 (8)
Change in Hb level from baseline to Week 12	0.28 ± 0.69 (4)	2.61 ± 2.20 (8)

Mean ± standard deviation (No. of subjects evaluated)

Table 52 shows the "change in Hb level from baseline to Week 12" in Study 301 by body weight. Hb levels tended to be higher in the danicopan group than in the placebo group in both body weight categories. The patient's body weight is therefore considered unlikely to affect the efficacy of danicopan.

Table 52. Change in Hb level (g/dL) from baseline to Week 12 by body weight
(Double-blind period: Interim Efficacy Analysis Set)

		Placebo	Danicopan
Body weight	≤60 kg	0.49 ± 0.62 (7)	3.01 ± 1.33 (8)
	>60 kg	0.73 ± 1.05 (13)	3.19 ± 1.28 (28)

Mean ± standard deviation (No. of subjects)

PMDA's view:

The results of efficacy analysis based on the latest data of Study 301 also showed no different trends between the entire population and the Japanese subpopulation. Therefore the conclusion on the efficacy of danicopan in Japanese patients with PNH remains unchanged. Since the change in Hb level from baseline to Week 12 did not differ between the body weight categories, the patient's body weight is unlikely to cause a clinically meaningful difference in the efficacy of danicopan.

The above PMDA's conclusion on the efficacy of danicopan was supported by the expert advisors.

1.2 Safety

At the Expert Discussion, the expert advisors supported the PMDA's conclusion described in Section "7.R.2 Safety" of the Review Report (1).

In view of the discussions at the Expert Discussion, PMDA concluded that the following precautionary statements should be included in the Warnings section of the package insert. The applicant responded appropriately.

Warnings

1 Danicopan inhibits the complement pathway and may therefore cause meningococcal infection, which can be fatal. Due attention should be paid to the following points:

1.1 During treatment with danicopan, the patient should be carefully monitored for early signs of meningococcal infection (e.g., pyrexia, headache, nuchal rigidity). If meningococcal infection is suspected, the patient should be examined immediately and appropriate actions such as antibiotic administration should be taken.

1.2 Prior meningococcal vaccination should be confirmed. If prior vaccination cannot be confirmed or additional vaccination is required, a meningococcal vaccine should be administered before the

start of treatment with danicopan. Additional meningococcal vaccination during treatment with danicopan should be considered as needed.

1.3 Meningococcal infection can be fatal. Danicopan should be administered under the supervision of a suitable physician at a suitable medical institution (i.e., both of which should be fully capable of managing emergencies), or in cooperation with a medical institution that can diagnose and treat meningococcal infection.

1.4 The risk of meningococcal infection should be explained to the patient to ensure their understanding of the early signs of infection. The patient should be cautioned to contact their primary physician if any related symptoms occur.

2 Danicopan should be administered under the supervision of a physician who has adequate knowledge of paroxysmal nocturnal hemoglobinuria only when the expected therapeutic benefits are considered to outweigh possible risks. Prior to the start of treatment with danicopan, its efficacy and associated risks, including the fact that danicopan does not completely cure the disease, should be clearly explained to the patient or their family to obtain consent.

1.3 Indication and dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusions described in Sections "6.R.2 Administration timing," "7.R.4 Indication," and "7.R.5 Dosage and administration" of the Review Report (1).

In view of the discussions at the Expert Discussion, PMDA concluded that the indication and dosage and administration of danicopan should be as follows (see below) and that the following precautionary statements should be included in the "Precautions Concerning Indication" and "Precautions Concerning Dosage and Administration" sections (see below). The applicant responded appropriately.

Indication

Paroxysmal nocturnal hemoglobinuria

Precautions Concerning Indication

1. Danicopan should be administered in combination with a complement (C5) inhibitor to patients with an inadequate response to appropriate treatment with a complement (C5) inhibitor.
2. Danicopan is considered to inhibit the serine protease activity of complement factor D, thereby inhibiting part of the complement-mediated infection-fighting mechanism. As a result, danicopan may increase susceptibility to meningococcal infection. Danicopan should be administered to eligible patients by a physician who fully understand its efficacy and safety after carefully assessing the appropriateness of the treatment. Prior to treatment with danicopan, prior meningococcal vaccination should be confirmed. If the patient has not received prior meningococcal vaccination or requires additional meningococcal vaccination, the patient should receive a meningococcal vaccine at least 2 weeks before the start of danicopan treatment, in principle.

Dosage and Administration

The usual adult dosage is danicopan 150 mg administered orally 3 times daily after meals in combination with a complement (C5) inhibitor. In patients with an inadequate response, the dose may be increased to a maximum of 200 mg.

Precautions Concerning Dosage and Administration

1. No clinical studies have been conducted to assess the efficacy or safety of danicopan in combination with other complement (C5) inhibitors than ravulizumab (genetical recombination) and eculizumab (genetical recombination).
2. Discontinuation of danicopan without tapering the dose may result in hepatic dysfunction. The dose of danicopan should be tapered over at least 6 days (100 mg 3 times daily for 3 days, followed by 50 mg 3 times daily for 3 days) before discontinuing the treatment. Dose tapering and discontinuation of danicopan should be performed while coadministering a complement (C5) inhibitor, in principle.
3. Dose tapering and discontinuation of danicopan may result in serious hemolysis. During dose tapering, the patient should be carefully monitored for hemolysis and accompanying symptoms, and appropriate actions should be taken as needed.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusion described in Section "7.R.6 Post-marketing investigations" of the Review Report (1).

In view of the discussions at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for danicopan should include the safety and efficacy specifications presented in Table 53, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 54 and 55.

Table 53. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• None	• Meningococcal infection • Infection (other than meningococcal infection) • Hepatic dysfunction • Serious hemolysis due to discontinuation of treatment with the product	• None
Efficacy specification		
• None		

Table 54. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey (all-case surveillance)	• Provision of information collected through early post-marketing phase vigilance • Preparation and provision of materials for healthcare professionals • Preparation and provision of materials for patients

Table 55. Outline of general use-results survey (draft)

Objective	To collect the safety and efficacy data of danicopan.
Survey method	All-case surveillance
Planned sample size	50 patients
Survey period	Date of approval to 7 years after approval
Registration period	Date of approval to 5 years after approval or the time point when 50 patients have been registered, whichever comes first
Observation period	1 year
Main survey items	• Patient characteristics: Age, sex, reason for use of danicopan, history of meningococcal infection, date of PNH diagnosis, findings of extravascular hemolysis, prior participation in clinical studies of danicopan, medical history, concurrent illness, etc. • Status of vaccination: Prior vaccination (meningococcal vaccine, pneumococcal vaccine, Hib vaccine) • Prior treatment for PNH: Blood transfusion (date of transfusion, number of transfusions, number of units) and other concomitant treatments • Status of danicopan treatment: Date of administration, dosage regimen (if changed or discontinued, the reason) • Efficacy: Change in LDH, change in Hb level, change in QOL, change in the number of units of blood transfusion • Laboratory tests: AST, ALT, LDH, bilirubin, etc. • Adverse events: Date of onset, seriousness, outcome, discontinuation of danicopan (yes/no), causal relationship to danicopan, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication at the dosage and administration shown below, under the following conditions. Since the product is an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Paroxysmal nocturnal hemoglobinuria

Dosage and Administration

The usual adult dosage is danicopan 150 mg administered orally 3 times daily after meals in combination with a complement (C5) inhibitor. In patients with an inadequate response, the dose may be increased to a maximum of 200 mg.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Since only a very limited number of Japanese subjects participated in the clinical studies of the product, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data from a certain number of patients have been accumulated, in order to identify the characteristics of these patients, to collect safety and efficacy data on the product without delay, and to take the necessary actions to facilitate the proper use of the product.
3. Prior to marketing, the applicant is also required to take necessary actions to ensure that the product will be administered under the supervision of a suitable physician at a suitable medical institution (i.e., both of which should be familiar with the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria and be fully capable of managing the risks, etc. associated with the product), in cooperation with a physician who is familiar with the diagnosis and treatment of meningococcal infection.

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
APH	Alternative pathway hemolysis
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
$AUC_{0\text{-}inf}$	AUC up to infinity
AUC_{tau}	AUC from time of administration to the end of the dosing interval
BCRP	Breast cancer resistance protein
BL	Base line
BSEP	Bile salt export pump
CC_{50}	50% cytotoxic concentration
CI	Confidence interval
CL_{cr}	Creatinine clearance
CL/F	Apparent clearance after administration of the drug
C_{max}	Maximum concentration
COVID-19	Coronavirus Disease 2019
CQA	Critical quality attribute
CTD	Common technical document
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
DMC	Data monitoring committee
Drug interaction guideline	"Guideline on drug interaction for drug development and appropriate provision of information" (PSEHB/PED Notification No. 0723-4 dated July 23, 2018)
EC_{50}	50% effective concentration
Eculizumab	Eculizumab (genetical recombination)
eGFR	Estimated glomerular filtration rate
FDA	U.S. Food and Drug Administration
FXR	Farnesyl X nuclear receptor
GC	Gas chromatography
Hb	Hemoglobin
hERG	Human ether-à-go-go-related gene
HPLC	High performance liquid chromatography
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IC-MPGN	Immune-complex membranoproliferative glomerulonephritis
IR	Infrared absorption spectroscopy
ka	Absorption rate constant
K_D	Equilibrium dissociation constant
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
MATE	Multidrug and toxic compound extrusion
MDR3	Multidrug resistance protein 3
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mITT	Modified intent to treat
MMRM	Mixed-effects model for repeated measures
MRP3	Multidrug resistance protein 3

MRP4	Multidrug resistance protein 4
MS	Mass spectrometry
MT_1	Melatonin receptor subtype 1
NMR	Nuclear magnetic resonance spectrum
NTCP	Sodium taurocholate co-transporting polypeptide
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PAR	Proven acceptable range
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	Paroxysmal nocturnal hemoglobinuria
Q/F	apparent inter-compartment clearance
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
Ravulizumab	Ravulizumab (genetical recombination)
S9	9000 g supernatant of liver homogenate
$t_{1/2}$	Elimination half-life
TID	Three times daily
T_{lag}	Lag-time
t_{max}	Time to reach maximum concentration
UGT	Uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
UV/VIS	Ultraviolet-visible spectroscopy
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution