22 February 2024
EMA/107893/2024, Corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Voydeya

International non-proprietary name: Danicopan

Procedure No. EMEA/H/C/005517/0000

## Note

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

[1] 07 March 2024

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# List of abbreviations

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AP | alternative pathway |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| bid | 2 times a day |
| BTH | breakthrough haemolysis |
| C3 | complement component 3 |
| C3G | complement 3 glomerulopathy |
| C5 | complement component 5 |
| C5i/C5is | C5 inhibitor(s) |
| CHMP | Committee for Medicinal Products for Human Use |
| $C_{max}$ | maximum observed concentration |
| COVID-19 | coronavirus disease 2019 |
| CP | classical pathway |
| CSR | clinical study report |
| CYP | cytochrome P450 |
| DART | developmental and reproductive toxicology |
| DDI | drug-drug interaction |
| eDISH | evaluation of drug-induced serious hepatotoxicity |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale |
| EVH | extravascular haemolysis |
| FACIT-Fatigue | Functional Assessment of Chronic Illness Therapy - Fatigue |
| FB | factor B |
| FD | factor D |
| GA | geographic atrophy |
| Hgb | haemoglobin |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IC-MPGN | immune-complex membranoproliferative glomerulonephritis |
| ISS | integrated summary of safety |
| IVH | intravascular haemolysis |
| LDH | lactate dehydrogenase |
| LFC | liquid-filled capsule |
| LP | lectin pathway |
| LS | least squares |
| LTE | long-term extension |
| MAA | marketing authorisation application |
| MAD | multiple ascending dose |
| mDISH | modified drug-induced serious hepatotoxicity |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed-effect model for repeated measures |
| NO | nitric oxide |
| OATP | organic anion transporting polypeptides |
| ODD | orphan drug designation |
| PD | pharmacodynamic(s) |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| PDCO | Paediatric Committee |
| PIP | paediatric investigation plan |
| P-gp | P-glycoprotein |
| PK | pharmacokinetic(s) |
| PNH | paroxysmal nocturnal haemoglobinuria |
| Pop-PK | population pharmacokinetic(s) |
| QoL | quality of life |
| QTc | corrected QT interval |
| RBC | red blood cell |
| RMM | risk mitigation measure(s) |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SCS | summary of clinical safety |
| SE | standard error |
| SMQ | Standard MedDRA Query |
| SOC | system organ class |
| TA | transfusion avoidance |
| TBIL | total bilirubin |
| TEAE | treatment-emergent adverse event |
| tid | 3 times a day |
| $T_{max}$ | time taken to reach maximum observed concentration |
| $t_{½}$ | terminal elimination half-life |
| TP1, TP2 | treatment period 1, 2 |
| TQT | thorough QTc |
| ULN | upper limit of normal |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Alexion Europe submitted on 28 February 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Voydeya, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 November 2019.

Voydeya, was designated as an orphan medicinal product EU/3/17/1946 on 12 December 2017 in the following condition: treatment of paroxysmal nocturnal haemoglobinuria.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Voydeya as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Voydeya

The applicant applied for the following indication:

*Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of signs or symptoms of extravascular haemolysis (EVH) in adult patients with paroxysmal nocturnal haemoglobinuria (PNH).*

## *1.2. Legal basis, dossier content*

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *1.3. Information on paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0403/2020 on the agreement of a paediatric investigation plan (PIP) including a waiver for the paediatric population from birth to 12 years of age and the granting of a deferral.

At the time of submission of the application, the PIP (EMEA-002310-PIP01-17) was not yet completed as some measures were deferred.

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report, addressing the possible similarity with authorised orphan medicinal products.

## *1.5. Applicant's requests for consideration*

### 1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

### 1.5.2. New active substance status

The applicant requested the active substance danicopan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

## *1.6. PRIME*

Voydeya was granted eligibility to PRIME on 14/11/2019 in the following indication: treatment of paroxysmal nocturnal haemoglobinuria.

Eligibility to PRIME was granted at the time in view of the following:

- The unmet need in the proposed condition is justified on the basis of chronic haemolytic anaemia, propensity of thromboembolic events and bonne marrow failure, while only a small number of affected patients respond adequately to existing treatments.
- The applicant has submitted preliminarily clinical observations in transfusion dependent patients, who responded to addition of the proposed product with a reduction in the number of transfusions;
- Therefore the potential of the product to significantly address the unmet need is considered justified.

Upon granting of eligibility to PRIME, Jorge Camarero Jimenez was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 22/04/2020. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- It was agreed with the applicant's plan to seek quality advice on general CMC Phase 3 SA, technology transfer between contract manufacturers of the drug substance, and validation plans for drug substance and drug product.
- It was recommended to seek scientific advice on the overall clinical pharmacology programme,
- It was recommended to discuss the paediatric plan in a scientific advice application.

## *1.7. Protocol assistance*

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 20 July 2017 | EMA/CHMP/SAWP/426022/2017 | Prof. Brigitte Blöchl-Daum and Dr Karin Janssen van Doorn |
| 30 January 2020 | EMA/CHMP/SAWP/26111/2020 | Dr Karin Janssen van Doorn and Dr |

| | | |
|---|---|---|
| | | Hrefna Gudmundsdottir |
| 25 June 2020 | EMA/CHMP/SAWP/316563/2020 | Ms Rosalia Ruano Camps and Dr Rune Kjeken |

***Scientific advice***

The applicant received scientific advice on three occasions, as mentioned in the table above for the development of Voydeya for treatment of paroxysmal nocturnal haemoglobinuria (PNH). The scientific advice pertained to the following quality, pre-clinical and clinical aspects:

- Starting materials, designation and testing and control of potential genotoxic impurities, drug substance and drug product specifications, stability testing plans for the drug substance, spray dried dispersion and drug product as well as proposed approach for establishing the shelf-life for the SDD, comparability demonstration of early vs. commercial manufacturing process, transfer of drug substance synthesis to commercial manufacturing site
- Non-clinical strategy, carcinogenicity studies, immunotoxicology studies, investigations regarding melatonin subtype 1 (MT1) receptor mediated off-target effects, mutagenicity testing, abuse potential
- Dose selection and investigation of hepatotoxic risk based on non-clinical and clinical data
- Clinical pharmacology programme
- Safety monitoring plan with focus on risk of infections and liver enzyme elevations
- Clinical proof of concept study: design, endpoints, population
- Single pivotal Phase 3 study: endpoints, study population, statistical analysis, dose justification, safety database

## *1.8. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Carolina Prieto Fernandez  Co-Rapporteur: Robert Porszasz

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Martin Huber

The appointed CHMP co-rapporteur had no such prominent role in Protocol assistance relevant for the indication subject to the present application.

| | |
|---|---|
| The application was received by the EMA on | 28 February 2023 |
| The procedure started on | 23 March 2023 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 28 June 2023 |
| The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 8 July 2023 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 3 July 2023 |

| | |
|---|---|
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 20 July 2023 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 07 September 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 27 October 2023 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 26 October 2023 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 9 November 2023 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 20 December 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 15 January 2024 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 25 January 2024 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 30 January 2024 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 08 February 2024 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Voydeya on | 22 February 2024 |
| Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS) | 22 February 2024 |
| The CHMP adopted a report on similarity of Voydeya with Aspaveli on (see Appendix on similarity) | 22 February 2024 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

Danicopan is intended for the treatment of signs or symptoms of extravascular haemolysis (EVH) in adult patients with paroxysmal nocturnal haemoglobinuria (PNH) as add-on to ravulizumab or eculizumab.

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired, rare, clonal and potentially life-threatening non-malignant hematologic disease characterized by complement-mediated red blood cell (RBC) haemolysis, with or without haemoglobinuria, an increased susceptibility to thrombotic episodes, and/or some degree of bone marrow dysfunction. The hallmark of PNH disease activity is complement-mediated haemolysis. The onset of PNH is often insidious. Although there have been reports of spontaneous remission, the course of the disease is generally chronically progressive.

### 2.1.2. Epidemiology

Epidemiologic studies in PNH are rare. Where data are available, the incidence has been reported to range from 0.08 to 0.57 per 100000 person years. Prevalence has been estimated to range from 1.04 to 3.81 per 100000 persons. In Europe or the United Kingdom (UK), the annual incidence of PNH has been reported as 1.3 to 2.98 per 1,000 000 (Korkama 2018; Hill 2016).

As of July 2017, according to the International PNH Registry population, the European population is well represented (3012/4439 patients from more than 30 countries located in Europe) and median age at disease onset for PNH was 35.5 years. Men and women were equally represented (female 53%) within the registry (Schrezenmeier 2020).

### 2.1.3. Biologic features, aetiology and pathogenesis

PNH is characterised by somatic mutation in the X-linked phosphatidylinositol glycan class A (PIG-A) gene. A single mutation of the PIG-A gene in bone marrow stem cells disrupts glycosylphosphatidylinositol (GPI) biosynthesis and results in a deficiency of all GPI-anchored proteins on the cell membrane and in the PNH phenotype. PIG-A deficient cells are rapidly eliminated by autologous complement activation leading to many of the clinical manifestations of the disease. Among the deficient proteins are the complement regulatory proteins CD55 and CD59. CD59 prevents terminal complement components from forming the haemolytic membrane pore, C5b-9 (the membrane attack complex). Absence of CD59 from PNH red cells results in intravascular haemolysis.

No universally accepted classification scheme is available, but the International PNH Interest Group (IPIG) classified PNH into 3 categories:

- classical PNH in which patients have clinical manifestations of haemolysis or thrombosis,
- PNH in the context of other primary bone marrow disorders such as aplastic anaemia or myelodysplastic syndromes,
- subclinical PNH in which patients have low proportions of PNH clones but no clinical or laboratory evidence of haemolysis or thrombosis.

The pathophysiology of PNH involves uncontrolled complement activation, resulting in intravascular haemolysis and extravascular haemolysis (EVH). Chronic, uncontrolled complement component 5 (C5) cleavage leads to production of C5a and C5b9, two powerful effectors that can damage blood cells, including lysis of red blood cells (RBCs). RBC haemolysis results in the release of intracellular free haemoglobin (Hgb) and lactate dehydrogenase (LDH) into circulation, irreversible binding to and inactivation of nitric oxide (NO) by Hgb and inhibition of NO synthesis, vasoconstriction and tissue-bed ischemia due to absence of vasodilatory NO as well as possible microthrombi manifesting as abdominal pain, dysphagia, and erectile dysfunction, platelet activation, and a proinflammatory and prothrombotic state.

### 2.1.4. Clinical presentation, diagnosis and stage/prognosis

PNH is characterized by destruction of RBCs (haemolytic anaemia), blood clots (thrombosis), impaired bone marrow function, and haemolysis. The typical clinical hallmark of PNH is complement-mediated intravascular haemolysis (IVH) of the RBCs (Schubert, 2015).

A substantial proportion of patients with PNH experience renal dysfunction and pulmonary hypertension. Patients also experience venous or arterial thrombosis in diverse sites, including the abdomen or central nervous system. Secondary effects, in addition to the risk of major end organ damage from thrombosis, include abdominal pain, extreme or unrelenting fatigue, difficulties in concentrating or thinking, and lower quality of life.

IVH in PNH releases cellular content into the surrounding environment leading to an increase in serum LDH level, which can be up to 10 times the upper limit of normal (ULN). IVH and the ensuing thrombosis is the major contributor to PNH morbidity and premature mortality. Before complement inhibitors such as eculizumab were developed, PNH patients usually survived for 10 to 22 years. The primary cause of death in these patients used to be thrombotic events. In the last 15 years the survival of PNH patients has improved by 75% and in some cases it is close to those without the disease (Gembillo et all, 2020).

Extravascular haemolysis (EVH) occurs as lysis outside of the circulation due to RBC opsonisation in the spleen or liver. It becomes a route of haemolysis when the terminal complement pathway is blocked by C5 inhibition.

### 2.1.5. Management

The current standard of care for PNH is treatment with eculizumab or ravulizumab (Kulasekararaj, 2022); both monoclonal antibodies that are designed to target C5 complement protein. Both are approved to treat adults and children with paroxysmal nocturnal haemoglobinuria in EU since 2007 and 2019 respectively.

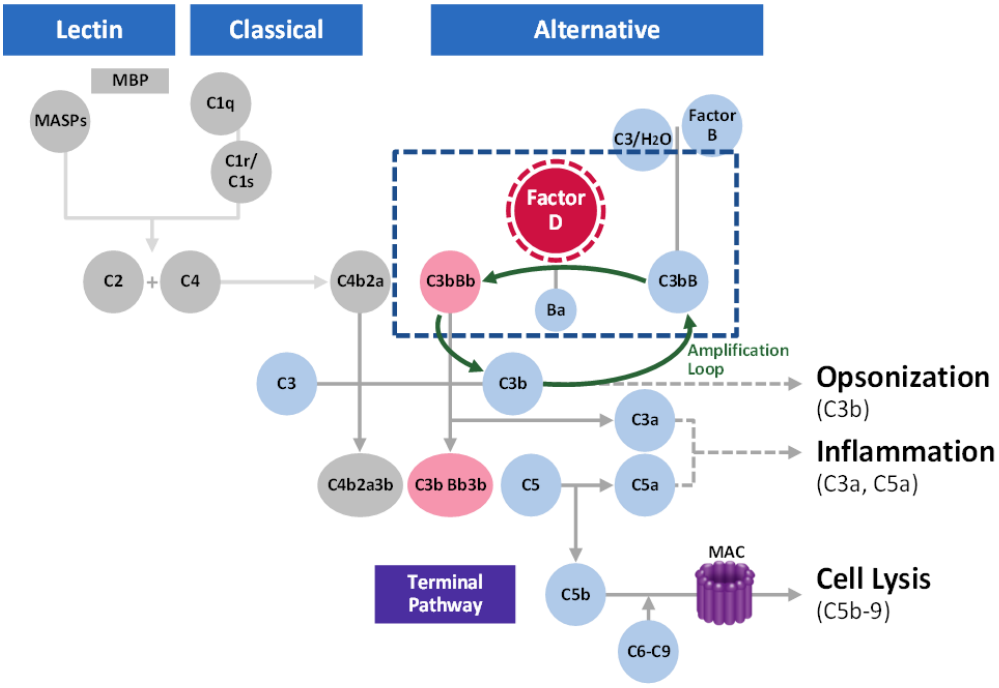
While IVH is controlled by C5 inhibition (as indicated by LDH < 1.5 × ULN), a small subset of patients with PNH who achieve durable IVH control and associated disease control with ravulizumab or eculizumab may experience emergence of clinically significant EVH. EVH is believed to be mediated C3 fragment deposition on PNH RBCs and is characterized by anaemia with low Hgb and elevated absolute reticulocyte counts (with or without transfusion requirements) and its associated symptoms such as fatigue and decreased quality of life. Clinically significant EVH occurs in approximately 20% of C5i treated patients, with approximately 10% of these patients requiring RBC transfusions.

The currently approved treatment for patients with PNH experiencing EVH is the C3 inhibitor pegcetacoplan (Aspaveli). Pegcetacoplan is approved in the EU as monotherapy for the treatment of adult patients with PNH who have haemolytic anaemia.

## *2.2. About the product*

Danicopan is a first-in-class oral small molecule reversible inhibitor of complement factor D (FD) that selectively blocks the complement alternative pathway (AP) but not the complement classical pathway (CP) or lectin pathway (LP). Danicopan is being developed for the treatment of PNH and other complement mediated diseases.

FD is a serine protease that catalyses the cleavage of complement factor B (FB) into Ba and Bb, which allows for the formation of the alternative pathway (AP) C3 convertase (C3bBb) (Figure 1).




Abbreviations: CX = complement component X; MAC = membrane attack complex; MASP = mannose binding lectin-associated serine protease; MBP = mannose-binding protein

**Figure 1: Complement pathway schematic**

The initially claimed indication for danicopan was:

*Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of signs or symptoms of extravascular haemolysis (EVH) in adult patients with paroxysmal nocturnal haemoglobinuria (PNH).*

The finally approved indication is:

*Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia (see section 5.1).*

The recommended starting dose of danicopan is 150 mg 3 times a day (tid) administered orally, approximately 8 hours apart (± 2 hours). Depending on clinical response, the dose can be increased to 200 mg tid.

## *2.3. Type of application and aspects on development*

The CHMP did not agree to the applicant's request for an accelerated assessment, as the product was not considered to be of major public health interest. This was based on the fact that - in the context of the evolving landscape and emergence of available treatments for the targeted patient population - it was unclear that danicopan as add-on to C5 inhibitors would address an unmet need in the applied indication. Further, as additional relevant data would need to be submitted during the ongoing procedure, this would hamper maintenance of a potential accelerated assessment timetable.

## *2.4. Quality aspects*

## 2.4.1. Introduction

The finished product is presented as film-coated tablets containing 50 and 100 mg of danicopan as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium laurilsulfate, magnesium stearate, hydrophobic colloidal silica and hypromellose acetate succinate

Film-coating: polyvinyl alcohol, titanium dioxide (E171), Macrogol 4000
and talc.

The product is available either in HDPE bottles with desiccant and child resistant seal, or in PVC/PCTFE/PVC blisters.

## 2.4.2. Active Substance

### *2.4.2.1. General information*

The INN of the active substance (AS) is danicopan and the chemical name is (2*S*,4*R*)-1-{2-[3-acetyl-5-(2-methylpyrimidin-5-yl)-1*H*-indazol-1-yl]acetyl}-*N*-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide. The molecular formula is $C_{26}H_{23}BrFN_7O_{32}$; and the relative molecular mass is 580.4 g/mol. The structure is shown in Figure 2.

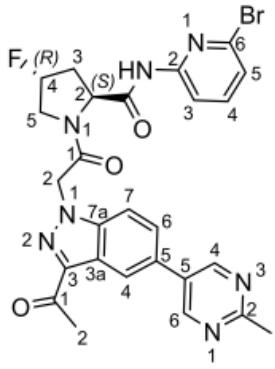



**Figure 2: Active Substance Structure**

The chemical structure of danicopan was elucidated by a combination of elemental analysis, UV spectroscopy, IR spectroscopy, mass spectrometry, $^{1}$H-, $^{19}$F- and $^{13}$C-NMR spectroscopy, and x-ray crystallography. The solid-state properties were investigated by XRPD, DSC, thermogravimetric analysis and dynamic vapour sorption.

Danicopan is a white/off-white to pale yellow powder in crystalline form. It is practically insoluble in water. The solubility in various solvents has also been studied.

The molecule has two stereochemical centres. Stereochemistry is defined by the starting materials and is maintained throughout the synthetic process.

Danicopan exhibits polymorphism. The thermodynamically stable Form II crystalline form is produced according to the proposed synthesis and isolation conditions. Test and acceptance criteria for the polymorphic form are included in the AS specification.

#### *2.4.2.1. Manufacture, characterisation and process controls*

Danicopan is manufactured in a multi-step convergent synthesis. The description of the manufacturing process and in-process controls is comprehensive. It includes the amounts of all raw materials, all the manufacturing operations, manufacturing parameters and in-process controls. The commercial batch size is provided.

The proposed starting materials (SMs) are supported by comprehensive information, in line with the requirements of ICH Q11 and are acceptable.

The impurity profile of each starting material, as well as the formation, fate and purge of impurities have been well-discussed. Impurities originating from the manufacturing process of the starting materials are sufficiently controlled. The specifications of each starting material are justified and also in line with the presented fate and purge discussion. The presented batch results demonstrate that there is no significant difference between the test results of AS batches manufactured from SMs of different origin.

Specifications and analytical results have been provided for all isolated intermediates. The batch results justify these limits.

Suitable specifications have been provided for all materials used in the manufacturing process. Fate and purge of residual reagents has been adequately discussed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities (organic impurities (process related and degradation products), mutagenic impurities, inorganic impurities, residual solvents and nitrosamines) were well discussed with regards to their origin and characterised.

Potential mutagenic impurities identified are sufficiently controlled under either option 2 or 4 of ICH M7. Potential secondary and tertiary amine impurities identified in the manufacturing processes, which should be considered in the finished product nitrosamine risk assessment were also discussed.

Data from forced degradation studies and stability studies confirm that the two stereocentres do not epimerise, these isomers are not degradation products and their level does not increase on storage under any of the conditions studied. The stability of the polymorphic form under forced degradation conditions was demonstrated.

The comprehensive process characterisation studies and parametric risk assessments informed the control strategy. Control for all the critical steps and intermediates has been established to ensure the identity, purity, and quality of each intermediate, and subsequently, to ensure a high quality active substance is produced by the commercial process.

The manufacture of danicopan does not involve aseptic processing and sterilisation, therefore no process validation is presented, this is acceptable.

The overall control strategy for the AS is acceptable.

There have been three iterations in the manufacturing process used to manufacture crystalline danicopan active substance for clinical studies, which are denoted process A, process B, and process C. There have been minimal changes across these three process iterations, as the synthetic route and sequence of bond forming steps has remained unchanged.

The differences across processes A, B, and C were clearly presented and justified. Results of batches (small and full scale) show comparability across all processes. They meet the specifications established for the active substance. Moreover, chromatographic impurity profile and XRPD can be considered similar.

Danicopan is packaged in two clear low-density polyethylene (LDPE) bags, head space is purged with nitrogen and each bag is secured with the plastic tie. This is stored with a clay desiccant in a rigid outer container. The LDPE bag meets the requirements of the applicable sections of 21 CFR (Part 182) and EU regulation 10/2011 for food contact materials. The desiccant is a non-contact packaging component.

#### *2.4.2.2. Specification*

The active substance specification includes tests for: description (visual), identification ($^1$H-NMR, HPLC), chiral identification (chiral HPLC), assay (HPLC), impurities (HPLC), chiral impurities (chiral HPLC), polymorphic form (X-RPD), residual solvents (GC-HS), palladium (ICP-OES), water content (KF) and residue on ignition (Ph. Eur.).

The specification parameters and limits have been set in line with ICH Q6A, Q3A, Q3C, as well as Ph. Eur. 2034 *Substances for pharmaceutical use* and the available batch and stability results, and fate and purge assessment and is considered acceptable.

Based on the maximum daily dose of 600 mg, according to ICH Q3A, the reporting threshold is 0.05%, identification threshold is 0.10% and the qualification threshold is 0.15%. The limits set for related substances are in line with these thresholds for most impurities, and all other related substances controlled higher than the qualification threshold are justified by toxicological qualification. Based on the *in silico* mutagenicity evaluation of impurity a specified impurity and the AMES tests of the analogous compounds, the proposed impurity limits are considered as acceptable.

Absence of a test for benzene (potential carry-over impurity) in the specification was justified by testing 3 representative Process C batches of danicopan. Routine testing is not required since the class 1 benzene solvent is less than 10% of the specified limit (NMT 2 ppm). Absence of tests for microbiological purity, elemental impurities and particle size has been sufficiently justified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines and adequately demonstrate the suitability of the methods for their intended purpose. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 6 commercial scale batches manufactured by the proposed commercial site and process were provided. The results are within the specifications and consistent from batch to batch. In addition, batch data from 20 batches of varying batch sizes manufactured both at the development and the commercial sites were presented. The results were generated according to analytical procedures in place at the time of manufacture and met the specifications in place at the time. The batches comply with the proposed specifications and demonstrate that the AS is produced in consistently good quality.

#### *2.4.2.3. Stability*

Stability data from seven batches of active substance of commercial or pilot scale, manufactured by processes B and C, stored in the intended commercial container closure system for up to 36 months under long term conditions (25ºC / 60% RH,) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

In addition, stability data from three batches from process A stored under the same conditions as above were presented. The process A active substance was stored in double low-density polyethylene (LDPE) bags inside an aluminium receptacle with a silica gel desiccant and closed with a lid.

The following parameters were tested: description, water content, assay, and related substances. The analytical methods used were the same as for release and are stability indicating. No change was observed under long term conditions for description, assay, and related substances. An increase in water content was observed for all batches but remained within specification and had no impact on the critical quality attributes such as assay and degradation products. Under accelerated conditions, the water content increase was still within specification limits.

A forced degradation study was performed to evaluate the solid-state and liquid state stability of the AS under various stress conditions according to ICH Q1A and ICH Q1B (photostability) guidelines. Data from control and stress conditions were provided. For solid state evaluation, appearance (visual), water content (KF), purity and impurities (HPLC), and X-ray powder diffraction (XRPD) measurement were performed. Based on the results of the forced degradation study, the purity and impurity HPLC method is suitable for use as a stability indicating method.

The AS is not photosensitive.

The purity and impurity results obtained from analysis of liquid samples treated under acidic, basic, and oxidative conditions were presented showing varying degree of degradation which was more prominent at alkaline conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months with storage condition "store below 30 °C", in the proposed container.

## 2.4.3. Finished Medicinal Product

#### *2.4.3.1. Description of the product and pharmaceutical development*

The finished product (FP) is presented as film-coated tablets containing 50, or 100 mg of danicopan. The description of the film-coated tablets is presented in Table 1. Different tablet strengths are distinguishable by size and debossing.

**Table 1: Description of Danicopan Film-Coated Tablets**

| Strength | Description |
|---|---|
| 100 mg | White to off-white round tablet approximately 13/32" (~10.3 mm) in diameter with 'DCN' above '100' debossed on one side and plain on the other side. |
| 50 mg | White to off-white round tablet approximately 5/16" (~8 mm) in diameter with 'DCN' above '50' debossed on one side and plain on the other side. |

The objective of development was to deliver danicopan immediate release 50 mg and 100 mg film-coated tablets for oral administration. In accordance with the ICHQ8, the CQAs of the product were

identified and were used as guidance during formulation and manufacturing process development studies to meet the QTPP (Table 2). The pharmaceutical development focused on those critical quality attributes (CQAs) that could be impacted by a realistic change to the finished product formulation or manufacturing process.

**Table 2: Quality Target Product Profile for Danicopan Tablets**

| Product Attribute | Commercial Target |
|---|---|
| Drug Substance Category | Small molecule |
| Dosage form and design | Oral Tablet, Immediate release film coated |
| Route of administration | Oral |
| Indication | Clinically significant extravascular hemolysis |
| Dosage Strength | 50 mg and 100 mg |
| Dosing Regimen | 150 mg dose given as: *1x100mg tablet and 1x50mg tablet or 3 x 50mg tablets*<br>200 mg dose given as: *2x100mg tablet or 4 x 50mg tablets* |
| Dosing Frequency | Three times daily (TID) |
| Compendia Requirements | Excipients must meet compendia requirements: USP/NF, Ph. Eur., and JP |
| Drug Product Quality Attributes | Must comply as per USP and ICH requirements for immediate release solid oral solid dosage forms |
| Container Closure System | Bottle: 60cc HDPE bottles with 1g desiccant<br>Blister: Single-cavity PVC/PCTFE/PVC blister |
| Storage Condition | Room temperature at ICH climatic zones I, II, III, and IV |
| Degradants and Related Substances | Below safety ICH threshold or qualified within commercial specifications.<br>Meets regulatory guidelines for genotoxic impurities from process or product |
| Microbial Limit Test | Meets compendia requirements: USP/NF, Ph. Eur., and JP |

ICH = International Conference on Harmonization; JP = Japanese Pharmacopeia;
NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

Danicopan is designated as a low solubility active substance according to the BCS Classification System (class 2). Key physicochemical characteristics of the AS (solid-state form particle size, solubility, degradation under stressed conditions) were adequately evaluated and the potential effect on the relevant properties was considered according to the ICH Q8 Guideline. Due to poor solubility of the AS, the aim of development was to provide an oral dosage form with improved solubility.

The initial formulation was liquid filled capsules (LFC); however due to crystallisation of the drug substance, it was decided to switch to a tablet formulation. In order to enhance solubility, a formulation containing amorphous, AS was sought.

The formulation development work for danicopan spray-dried dispersion (SDD) finished product intermediate involved assessing the feasibility of producing amorphous SDD with danicopan and identifying a suitable stabilising polymer and processing solvent to produce a physically and chemically stable SDD with an appropriate drug load.

Various polymers and AS loading were evaluated using miscibility assessment, supersaturation studies. The final polymer was selected based on relative bioavailability in dog studies and the ratio of AS to polymer was refined using *in vivo* dog data.

No effect of particle size of the SDD was observed on dissolution characteristics of the finished product. However, in the intermediate specification of SDD, a particle size limit is included based on the historical data of 18 batches that had acceptable content uniformity results. It was also demonstrated that SDD particle size does not change during storage.

Formulation variants with different fillers were studied and lactose monohydrate and microcrystalline cellulose were selected for further tablet development with the HPMCAS based SDD system.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The choice, characteristics and function of the excipients have been discussed. Compatibility of the active substance with the excipients has been demonstrated in formulation development studies and long-term stability studies.

Intragranular and extra-granular excipient blendings were optimised for roller compaction. A design of experiments (DoE) study was performed to evaluate formulation robustness for the roller compacted common blend used to manufacture Danicopan 50 mg and 100 mg film coated tablets. The AS form, excipients, and composition were determined to be robust based on the results of development and formulation studies.

Danicopan film coated tablets, 50 mg and 100 mg, are dose proportional and are manufactured by a common blend. There are no overages used in the formulation of Danicopan film-coated tablets. The tablets have been used in throughout clinical studies and monitored for accelerated and long-term stability under ICH conditions.

A relative bioavailability study was conducted to assess tablet formulation against clinical LFC formulations. This *in vivo* data suggested that the bioavailability of the tablet formulation under fed conditions is almost equal to that of the LFC. Considering all the available bioavailability and stability data, a decision was made to move ahead with the danicopan film coated tablet formulation for clinical studies.

Dissolution was identified as CQA of danicopan tablet product performance that could be potentially impacted by process and formulation variation.

A dissolution method which achieved sink conditions has been selected as the most appropriate. The chosen dissolution method development followed the guidance in ICH Q6A and adequately justified. The selected apparatus, medium, pH, stirring speed and surfactant were adequately justified.

The discriminatory power of the method was investigated by comparing the dissolution profiles for the formulation robustness batches, comparing uncoated and coated tablet dissolution and residual crystallinity. There is no significant difference in the dissolution profiles of the core tablets and film coated tablets.

Discriminatory power of the dissolution method has been demonstrated with respect to meaningful changes in tablet composition and process parameters.

Studies were performed to evaluate the robustness of the core tablet manufacturing step and the film coating step. The purpose of the core tablet manufacturing process robustness DoE study was to evaluate the effects of the roller compaction, blending, and compression processing parameters on the manufacturability and CQAs of the finished products.

Moreover, a coating study was designed and performed to establish the PARs for the film coating process using debossed core tablets. The coating and the analytical results for the coating study confirmed the film coating process is robust and the film coated tablets met the finished product release specifications.

Based on the output of the initial assessment, additional risk mitigation work was performed to establish a thorough understanding of the manufacturing process and aid in appropriate optimisation for future manufacture. After comprehensive experimentation, the initial risk assessment was updated in line with the enhanced process understanding, and the appropriate proven acceptable ranges (PARs) of process parameters are defined. These studies were used to establish the parameter ranges, the in-process controls and the control strategies for the SDD and the finished product.

Two different container closure systems are proposed:

- High-density polyethylene (HDPE) bottle with silica desiccant and polypropylene child resistant (CR) screw cap

- Blister which consists of a tri-layer film of Polychlorotrifluoroethylene (PCTFE) sandwiched between polyvinyl chloride (PVC) layers (PVC/PCTFE/PVC), sealed with push through lidding foil.

The materials comply with Ph. Eur. and EC requirements. The choice of the container closure systems has been validated by stability data and they are both adequate for the intended use of the product.

#### *2.4.3.1. Manufacture of the product and process controls*

The FP is manufactured through in 6 main steps: solution preparation, spray drying, secondary drying, dry granulation, compression, film coating.

A clear narrative description of the manufacturing process was included as was a flow-chart, which also shows the in-process controls. The process is considered a standard manufacturing process.

Critical steps and their control were clearly presented. In-process controls have been justified. Moreover, reference to methods used for the in-process controls have been included in the corresponding specifications table.

The process intermediates were defined and are controlled by suitable specifications. The container closure system for each of the intermediates was described. Proposed holding times are supported by data and are acceptable.

A clear validation protocol has been submitted. Process validation of the spray dried dispersion and finished product manufacturing processes will be completed prior to the launch of finished product from the commercial manufacturing sites using the manufacturing processes as described in the dossier and that the validation batches will be manufactured according to an approved process validation protocol. This is acceptable.

#### *2.4.3.2. Product specification*

The finished product release and shelf-life specifications for 50 and 100 mg, include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV), assay (HPLC), degradants/impurities (HPLC)(LC-MS), uniformity of dosage units (Ph. Eur.), dissolution (HPLC-Ph. Eur.), form characterisation (XRPD), moisture content (KF), microbial examination (Ph. Eur.).

The specification is based on the ICH Q6A, development history, batch analysis, clinical relevance, stability data, and toxicological qualification. Regarding degradation products, limits for specified impurities, unspecified impurities and total impurities at release and at shelf-life comply with ICH Q3B.

The potential presence of elemental impurities (EIs) in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. An overall risk assessment for elemental impurities has been presented, considering the sum of all contributions

of relevant sources to elemental impurities in the FP. The assessment is based on actual maximum levels of EIs per component and show that none is likely to be present in the finished product above the control threshold (i.e. 30 % of the established PDE). The analytical method has been correctly described and suitably validated for its intended purpose. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment to evaluate the potential for nitrosamine impurities in the finished product considering all suspected and actual root causes was performed in accordance with the latest guideline *EMA Questions and Answers on Information on nitrosamines for marketing authorization holders* (*EMA/409815/2020*). The assessment concluded that there is a theoretical risk of nitrosamine formation, and hence representative batches of FP were tested for four specific nitrosamines. Confirmatory testing with the validated method was conducted to discharge the potential risk highlighted. Four representative batches of danicopan film coated tablets were tested for the identified potential nitrosamines and results were reported at less than 3 ppb level.

However, the originally proposed limit for one of the four tested nitrosamine impurities was not acceptable. In addition, the correct maximum daily dose established in the SmPC was not considered in the calculations. Furthermore, the details of the analytical methods used were missing. As a result, the CHMP raised a Major Objection requesting revision of calculations, tightening of initially proposed limit for this particular impurity, and sufficient details for the analytical methods. In their response, the applicant accepted the tighter limits for the impurity in question, considered the correct maximum daily dose in the calculation of the AI limit for the three common nitrosamines and provided additional batch data and presented the missing details of the analytical methods, while the testing method was also optimised to increase sensitivity. They have also demonstrated that each of three small molecule nitrosamines were not detected and given the LoQ of the method, not present above 10% of the respective acceptable intake.

In conclusion, the overall data warrants the inclusion of one specified nitrosamine impurity only in the FP specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Analytical method validation studies for non-pharmacopoeial analytical methods have been conducted and, accordingly, the validation reports are provided, as per ICH Q2. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 25 batches of commercial or pilot scale for each strength throughout the whole development programme and including 14 used for phase III clinical studies and stability batches. Results met the specifications in place at the time and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

### *2.4.3.3. Stability of the product*

Stability data from three commercial scale batches of each strength manufactured with AS from process C (commercial process) stored for up to 12 months under long term conditions (25ºC / 60% RH) and under intermediate conditions (30°C/75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches were packed in both types of primary packaging proposed for marketing.

Supportive stability data from three commercial scale batches of each strength manufactured with AS from process B stored for up to 24 months under long term conditions (25ºC / 60% RH) and under

intermediate conditions (30°C/75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches were packed in two types of primary packaging (blisters and bottles), which are considered to be sufficiently representative to leverage the primary stability data to support the proposed shelf life.

Samples were tested for description, moisture, assay, degradation products, dissolution, crystal form and microbial contamination. The analytical procedures used are stability indicating. The results comply with the proposed specification limits. No significant changes have been observed.

Samples in either of the two bottle types and in either of the two blister types under long-term and intermediate conditions show little or no change in description, assay, degradation products, dissolution or microbiological quality. No trend in assay and degradation products were observed for any of the batches and storage conditions. An increase in moisture was observed but remained within the specification.

A photostability study conducted according to ICH Q1B option 2 on two batches demonstrated that the product is not photosensitive.

An in-use stability study has been carried out for two batches, at 25ºC/60% RH with desiccant and at 30ºC/75% RH without desiccant. Results remained within the specification limits although as expected, water content increased in these tablets exposed to high humidity (75% RH). Results confirmed that the product is chemically and physically stable and an in-use stability of minimum 48 days for actual patient use as stated in SmPC section 6.3 can be supported.

Moreover, forced degradation studies were carried out under heat, oxidative (30% hydrogen peroxide), basic (1N NaOH), acidic (1N HCl), and light (ICH Q1B) stress conditions. The results confirmed that the identification, assay and related substances methods are stability indicating.

Based on available stability data, the proposed shelf-life of 30 months in HDPE bottles and 2 years in PVC/PCTFE/PVC blisters without any special storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

#### *2.4.3.4. Adventitious agents*

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products. A manufacturer's BSE/TSE statement is included.

## 2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A major objection raised during the procedure concerning the information regarding the risk assessment on the potential presence of nitrosamine impurities has been resolved by provision of additional data. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## 2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

## 2.4.6. Recommendation(s) for future quality development

Not applicable.

# *2.5. Non-clinical aspects*

## 2.5.1. Introduction

Danicopan (also ALXN2040 or ACH-0144471) is an orally administered small molecule, which is proposed to inhibit complement Factor D (FD). This protein is a serine protease required for the formation of C3 convertase, via cleavage of factor B, a rate limiting enzyme in complement alternative pathway (AP) activation and amplification. FD is a key component of alternative pathway as it is required for its activation as well as amplification activity. Nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies with danicopan have been conducted to support the use of danicopan to treat PNH in human. Pivotal safety pharmacology and toxicology studies were conducted in accordance with Good Laboratory Practice (GLP) regulations.

## 2.5.2. Pharmacology

### *2.5.2.1. Primary pharmacodynamic studies*

Pharmacological actions of danicopan were investigated in in-vitro, ex-vivo and in-vivo systems. With this aim, binding to the intended pharmacological target (FD) was shown to be reversible and with a nanomolar affinity ($K_D$ = 0.00054 μM). From the in-vitro assays it was concluded a direct action on the enzyme rather than with the substrate C3bB complex, as inhibitory action was also reported against the minimal substrate (small synthetic thioester substrate). The in vitro characterisation of danicopan also included the inhibition of complement AP activity, although it did not inhibit components of the complement CP and LP, which was shown in haemolysis and Wieslab functional assays.

Furthermore, the inhibition of complement AP activity in sera from pharmacologically active species was analysed (study ACH-15-088), resulting in $IC_{50}$ values of 0.43 μM (haemolysis assay in Beagle dogs) and 0.078 μM and 0.066 μM (haemolysis and Wieslab respectively in cynomolgus monkeys). It is noted that haemolysis assay resulted in an order of magnitude lower in the case of cynomolgus monkeys (ACH-15-088). Then in a further study (ACH-15-089), the applicant presented the results of the potency to inhibit AP, in which different potency between dog and human was not confirmed. In the same study, inhibitory potency was also dissimilar when comparing human and monkey results.

Additional data submitted during the procedure regarding the inter-species difference in danicopan potency as an AP inhibitor showed that with activity in human serum as benchmark, danicopan is more potent in monkey serum, less potent in beagle dog serum by no greater than 5.2-fold, and less-potent in rabbit serum by no greater than 8.7-fold. In contrast, danicopan is not pharmacologically active in mouse or rat serum.

Regarding the variation in danicopan potency within a species it was shown that the $IC_{50}$ values range by approximately 24-fold and 19-fold among the 20 individual human samples, approximately 5.6-fold and 14-fold among the 10 cynomolgus monkey samples, and approximately 7.0-fold among the 10 beagle dog samples.

From the ex vivo studies, by using plasma samples of monkeys, the applicant concluded that inhibition of AP activity can be obtained at danicopan plasma concentration of 150 ng/mL. However, in correlation with the in vitro studies, danicopan's potency was lower in dogs and rabbits (EC50 range from 197.8 to 555 ng/ml in dogs, and EC50 = 1285 ng/ml in rabbits).

#### *2.5.2.2. Secondary pharmacodynamic studies*

Potential off-target actions were analysed in an *in vitro* panel of 55 targets. The results of this analysis presented a potential effect of danicopan on A1 and A3 adenosine, and MT1 melatonin receptors. Also a potential in vitro effect on hCav1.2 calcium channel was observed. Further assessments (neurobehavioural and CV) in *in vivo* studies did not reveal significant effects in animals.

Results related to BSEP, MDR3, UGT1A1 and UGT2B7 are shown in the DDI section. It is noted that a potential disruption of bile acid homeostasis was reported (see Toxicology section).

Five metabolites of danicopan were identified and assessed in primary pharmacodynamics, cellular toxicity and mitochondrial toxicity. Four metabolites (ACH-0144709, ACH-0145069, ACH-0145071, and ACH-0145072) were tested for AP inhibition by haemolysis assay and had little or no inhibitory activity against serum AP activity ($IC_{50}$ > 1 µM) (ACH-16-065; RTR-0065), in contrast to danicopan ($IC_{50}$ = 0.027 µM) (ACH-15-086). Danicopan metabolites also showed little potential for cytotoxicity (2 metabolites tested) and mitochondrial toxicity (4 metabolites tested). These compounds, products of amide hydrolysis and/or carbonyl reduction, represent the most prominent metabolites *in vitro* and *in vivo* in nonclinical species and humans.

Additional *in vitro* studies showed that antibacterial activity is not related to AP activity, indicating danicopan with a lower risk of infections than C3 and C5 inhibitors.

#### *2.5.2.3. Safety pharmacology programme*

Both *in vitro* and *in vivo* safety pharmacology studies were conducted with danicopan, no significant findings were reported.

Although an elevated heart-rate has been reported in a tolerability study (750 mg/Kg/day), this effect was attributed to an incidental finding, given that no similar effect was observed in the GLP study at higher doses (1000 mg/Kg/day).

#### *2.5.2.4. Pharmacodynamic drug interactions*

In these studies, potential interactions of danicopan were evaluated with complement inhibitors FUT-175, compstatin, and an anti-C5 antibody (eculizumab), and then analysed by AP-dependent rabbit cell haemolysis and AP Wieslab assay (ACH-15-100), or AP-dependent haemolysis of erythrocytes from a PNH patient (ACH-17-073). Synergistic interactions were observed in the case of eculizumab. No antagonist activity was reported.

### 2.5.3. Pharmacokinetics

*In vitro* and *in vivo* studies were performed to characterise the PK profile of danicopan.

Bioanalytical methods in the non-clinical section are presented as validated or partially validated meeting to the requirements. Additional data were submitted regarding in study validations or studies ACH-15-036, ACH-15-039, ACH-15-040, ACH-15-044, ACH-15-045, and ACH-15-161 (results not shown here).

In terms of absorption of danicopan, it presented moderate to high *in vivo* clearance, moderate steady state volume of distribution, a short terminal half-life (0.8-1.5 h IV, 1.6-3.4 h oral), and low to moderate oral bioavailability (15.8% to 38.7%).

It is noted the information submitted by the applicant in this section is limited, only a brief discussion can be found for 28-day and 14-day repeat dose toxicity studies in rats and dogs, respectively. Also in this section, several formulations are mentioned to be used in the nonclinical studies.

Distribution studies displayed a wide presence of danicopan to tissues, including also melanin-containing tissues, which was further investigated in phototoxicity studies (other studies section). Moderately high plasma protein binding, mainly in albumin, and moderate distribution into blood cells was reported. Danicopan was also detected in placental and lactation phases in the *in vivo* studies, which has been accordingly included in section 5.3 of SmPC.

Metabolic pathways of danicopan were investigated in hepatocytes. The main metabolic pathway was identified to be the amide hydrolysis in the rat (58.6%), dog (84.4%), and human (83.7%); and carbonyl reduction plus a combination of carbonyl reduction/amide hydrolysis in the monkey (84.1%). With regards to the oxidative metabolism, the relevance in humans was only 0.8%, whereas rat, dog and monkey showed 41.4%, 15.2% and 1.6%, respectively. Although metabolite M426 has been detected above 10% in plasma samples, it can be qualified from a toxicological point of view, given that in dogs was found at similar levels to human samples.

The ADME studies indicated that most of danicopan was recovered in faeces followed by urine, both in rat and dog species.

DDI *in vitro* studies showed a minimal contribution of CYP based metabolism of danicopan. However, the results showed that danicopan has the potential to interact with several of the transporters evaluated. In this context, danicopan inhibited a panel of transporters with an IC50 of 5.72 µM for BCRP, 3.96 µM for Pgp, 27.4 µM for OCT2, 10.8 µM for OATP1B1, 19.9 µM for MATE1, 11.6 µM for MATE2-K, and 23.9 µM for BSEP. The IC50 values for OAT3, OATP1B3, and MRP2 were > 30 µM. Danicopan did not inhibit OAT1.

Further analysis of bile disposition were carried out by using radiometric assays in vesicles containing human BSEP and MRP2, MRP3 and MRP4, NTCP in MDCK cells, dog Bsep and Mrp2 in vesicles, and MDR3 in human hepatocytes. In addition, bile disposition was assessed using LC-MS/MS in Bsep/BSEP in rat, dog, and human hepatocytes and using a luminescence intensity assay in FXR. Results from these studies revealed the potential of danicopan to interact with human BSEP, MRP2, MRP3, MRP4, MDR3, sodium taurocholate co-transporting polypeptide (NTCP), FXR, dog Bsep and Mrp2, and rat Bsep. In addition, danicopan has shown the potential to disrupt bile acid homeostasis in SCHH.

## 2.5.4. Toxicology

### *2.5.4.1. Single dose toxicity*

No dedicated single-dose toxicity studies were conducted.

#### *2.5.4.2. Repeat dose toxicity*

Chronic repeat administration of danicopan to rats resulted in the identification of target organs of toxicity, such as adrenal gland (hypertrophy), liver (centrilobular hypertrophy in males and females at all dose levels, cytoplasmic granules in the hepatocytes and/or Kupffer cells in females at all dose levels, basophilic cellular alteration in females at all dose levels and single cell necrosis of hepatocytes in 2 females at 500 mg/kg/day), and thyroid (thyroid follicular cell hypertrophy in males and females at all dose levels, and follicular cell adenoma in the thyroid of a single female given 500 mg/kg/day). The applicant considered the findings reported in these tissues as an adaptive response to increased metabolic enzyme production, mainly in liver.

Findings in adrenal glands (weight changes and histopathology analysis) were considered related to stress. Further proliferation leading to adenomas and later carcinomas of the thyroid has been described as rodent specific. In rats, exposure was generally higher in females compared to males.

Although other non-rodents were shown to be pharmacologically relevant for danicopan, the selected non-rodent species for the toxicology assessment of danicopan was dog species (although inhibition of AP activity was estimated in monkeys). Chronic studies in dogs (13-week and 39-week in duration) showed liver as the main target organ of toxicity. Also thymus and (lymphoid depletion) and adrenal glands (cortical hypertrophy) were identified as potential target tissues. Hepatic injury (increases in AST, ALT, ALP, GGT activities and in total, direct and indirect bilirubin concentrations) included bile duct hypertrophy/hyperplasia, pigment accumulation in Kupffer cells and hepatocytes were observed in the three studies conducted. In the 39-week toxicity study, danicopan at the dose of 150 mg/kg/day was not tolerated due to cholestatic liver injury. Hypertrophy/hyperplasia of the bile duct was observed in males at greater than or equal to 75 mg/kg/day.

#### *2.5.4.3. Genotoxicity*

Danicopan was not genotoxic in the Ames bacterial reverse mutation assay, *in vitro* micronucleus assay in human peripheral blood lymphocytes or in the *in vivo* micronucleus assay in rats.

#### *2.5.4.4. Carcinogenicity*

Danicopan was not carcinogenic in the 6-month carcinogenicity study in TgRasH2 mice and in the 2-year rat carcinogenicity study. However, in the rat study a higher incidence of endometrial epithelium neoplasm at the highest dose of 500 mg/kg/day compared to control animals was observed although the rat strain can have a high background incidence of endometrial carcinomas. The clinical relevance of this finding is unknown.

#### *2.5.4.5. Reproductive and developmental toxicity*

Rabbit species was selected for DART studies, based on the absence of pharmacological activity of rats. Considering the fertility studies conducted in rabbits, NOAEL for male and female reproductive toxicity was established by the applicant at 250 mg/kg/day, considering the poor male and female reproductive performance at 500 mg/kg/day.

EFD toxicity assessment revealed mortality and abortion at 1000 mg/Kg/day (mean body weight losses and lower mean body weight gains with corresponding reduced mean food consumption and decreased defecation). Thus, NOAEL value for maternal toxicity and EFD toxicity was considered for rabbits to be 500 mg/Kg/day, based on findings of decreased maternal and foetal body weight and maternal body

weight gain and food consumption. In rats, a non-pharmacologically relevant species, the NOAEL for maternal toxicity and EFD toxicity were 1000 and 500 mg/Kg/day, respectively.

Information related to reproductive and developmental toxicity is shown in the SmPC.

NOAEL value in the PPND study conducted in rabbits was established at 250 mg/kg/day, the maximum dose tested in the study. The applicant presented the results of a DRF JAS in dogs, although no definitive JAS is shown in the dossier. It is noted that changes observed in juvenile dogs were comparable to those observed in adult animals (hepatobiliary toxicity consisted in hypertrophy/hyperplasia of the bile ducts, usually accompanied by portal mixed cell infiltration, and acute degeneration/necrosis of bile ductal epithelium).

#### *2.5.4.6. Toxicokinetic data*

Toxicokinetic data were shown in the repeat dose toxicity studies section.

The applicant has reported Beagle dogs and Wistar rats in the interspecies comparison, showing lower safety margins in the case of dogs (danicopan is not pharmacologically relevant in rats).

#### *2.5.4.7. Local tolerance*

Considering the intended route of administration is oral route, the absence of dedicated studies is acceptable.

#### *2.5.4.8. Other toxicity studies*

The lack of antigenicity, immunotoxicity and dependence studies is acceptable.

As for the metabolite 2-amino 6-bromopyridine is also an impurity (ACH-0144240). Ames test for this molecule was also included in the section 3.2.r (regional section). The specified impurities (ACH-0144614, ACH-0145607, ACH-0146345, and ACH-0144769) have been qualified in toxicology studies.

Danicopan was excreted into the milk of lactating rabbits following oral administration from lactation Day 4 to 10, with milk concentrations approximately 5 and 3.5 times higher compared to maternal plasma concentrations at 50 and 250 mg/kg/day, respectively.

Negative results for danicopan were obtained in the *in vivo* phototoxicity study.

## 2.5.5. Ecotoxicity/environmental risk assessment

Environmental Risk Assessment of danicopan was determined in line with the current guideline (EMEA/CHMP/SWP/4447/00). According to the data and studies provided by the applicant, danicopan is unlikely to pose a risk for the environment.

**Table 3: Summary of Main Study Results**

| **Substance (INN/Invented Name):** | | | |
|---|---|---|---|
| **CAS-number (if available):** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | $LogD_{OW}$ = 3.24 at pH 5<br>$LogD_{OW}$ = 3.17 at pH 7<br>$LogD_{OW}$ = 3.11 at pH 9 | >4.5 Potential B<br>>4.5 PBT (**N**) |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |

| | | | |
|---|---|---|---|
| Bioaccumulation | log $D_{ow}$ | 3.11-3.24 | Not B; not PBT or vPvB |
| Persistence | DT50 | N/A | |
| Toxicity | NOEC | N/A | |
| **PBT-statement:** | The compound is not considered as PBT nor vPvB | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default or refined (e.g. prevalence, literature) | Fpen = 0.0000017<br>PEC = 0.00051 (refined) | μg/L | > 0.01<br>No phase II required |
| Other concerns (e.g. chemical class) | | | **N** |
| ***Phase II Physical-chemical properties and fate*** | | | |
| **Study type** | **Test protocol** | **Results** | **Remarks** |
| Water solubility | OECD 105 | *17.5 mg/L* | 20ºC ± 1ºC |

## 2.5.6. Discussion on non-clinical aspects

**Pharmacology**

Primary pharmacodynamic effects on FD protein (pharmacological target) were shown to be reversible and within the range of nanomolar (KD = 0.00054μM). Also in the *in vitro* studies, the mechanism of action proposed was a direct action on the enzyme rather than with the substrate C3bB complex. No direct action on the complement CP and LP was concluded.

Furthermore, the inhibition of complement AP activity in sera from pharmacologically active species was analysed (study ACH-15-088), resulting in IC50 values of 0.43 μM (haemolysis assay in Beagle dogs) and 0.078 μM and 0.066 μM (haemolysis and Wieslab respectively in cynomolgus monkeys). The significant variability noted inter- and intra-species was attributed to the intrinsic AP activity for each individual. This aspect should be considered for the interpretation of the pharmacological data, considering the potential uncertainty when results are interpreted.

From the ex vivo studies conducted with plasma samples of monkeys, the applicant concluded that that at least 80% inhibition of AP activity can be achieved when plasma danicopan is ≥ 150 ng/mL (EC50 = 31.27 ng/ml). However, in correlation with the *in vitro* studies, danicopan's potency was lower in dogs, and rabbits (EC50 range from 197.8 to 555 ng/ml in dogs, and EC50 = 1285 ng/ml in rabbits).

Secondary pharmacodynamic investigations reported potential effects of danicopan on A1 and A3 adenosine, and MT1 melatonin receptors. It is noted that IC50 value for MT receptor in rats was one order of magnitude higher than for humans. This aspect should be taken into account for humans, given that danicopan has shown to be accumulated in melatonin containing tissues. Further assessments (neurobehavioural and CV) in *in vivo* studies did not reveal significant effects in animals.

Both *in vitro* and *in vivo* safety pharmacology studies were conducted with danicopan, resulting in no significant findings. Only an elevated heart-rate was reported in a tolerability study (750 mg/Kg/day), but it was considered as an incidental finding, given that no similar effect was observed in the GLP study at higher doses (1000 mg/Kg/day).

Also as part of the pharmacological characterisation, pharmacodynamic interaction studies were conducted to justify the potential clinical utility of the combination of danicopan and complement inhibitors (i.e. eculizumab).

**Pharmacokinetics**

The bioanalytical assays of the pivotal toxicological studies were carried out at the same test facility where the validations were performed, accordingly, no cross-validations were necessary. The in-study

(assay-) validations were appropriate, but no ISR were done in all studies. In the case of the non-pivotal studies, such as dose finding studies, formulation finding studies, and some of the PK studies can be hardly accepted. These BA assays were performed mainly by the sponsor (Achillion Pharmaceuticals, Inc.), and the study reports declared that the bioanalytical methods used were qualified, and the calibration and QC standards met the acceptance criteria, but no individual calibration and QC standard results (i.e., in-study validation) were reported. In spite of the uncertainties detailed previously, sufficient information was provided for the in-study validation of the studies above, and it can be supposed that similar results are also available for the other non-pivotal studies.

ADME characterisation concluded moderate to high *in vivo* clearance, moderate steady state volume of distribution, a short terminal half-life (0.8-1.5 h IV, 1.6-3.4 h oral), and low to moderate oral bioavailability (15.8% to 38.7%).

It is noted the information submitted by the applicant in this section is limited, only a brief discussion can be found for 28-day and 14-day repeat dose toxicity studies in rats and dogs, respectively. No relevant data related to absorption in the pivotal studies (6- or 9-month) is included in this section. Furthermore, the applicant mentions that detailed results of studies are presented in the IB. At this point, the applicant is supposed to know that this is a Marketing Authorisation Application.

Different formulations were used in preclinical and clinical studies. Both dog and rat species were administered with danicopan as a suspension, while the formulation selected for clinical practice was finally an immediate release tablet. The Applicant was requested to elaborate a comparative table with pharmacokinetic parameters obtained with different formulations and species. Safety margins for clinical use of 150 mg and 200 mg tablets 3 times a day (tid) were calculated using the steady-state exposures in the pivotal Phase 3 study (ALXN2040-PNH-301).

Distribution studies displayed a wide presence of danicopan into tissues, moderately high plasma protein binding, mainly in albumin, and moderate distribution into blood cells was reported. Danicopan was also detected in placental and lactation phases in the *in vivo* studies, which has been accordingly included in section 5.3 of SmPC.

Metabolism of danicopan was investigated in humans and non-clinical species. The most relevant aspect of metabolism was the relevance of the oxidative metabolism between species, showing only 0.8% in humans, and 41.4%, 15.2% and 1.6% in rat, dog and monkey respectively. This issue should be also considered in the discussion for species selection.

For metabolite M426, it could be qualified from a toxicological point of view, given that in dogs was found at similar levels to human samples.

In terms of excretion, danicopan was excreted in faeces followed by urine, both in rat and dog species.

DDI *in vitro* studies showed a minimal contribution of CYP based metabolism of danicopan. On the contrary, danicopan inhibited a panel of transporters with an IC50 of 5.72 µM for BCRP, 3.96 µM for Pgp, 27.4 µM for OCT2, 10.8 µM for OATP1B1, 19.9 µM for MATE1, 11.6 µM for MATE2-K, and 23.9 µM for BSEP. The IC50 values for OAT3, OATP1B3, and MRP2 were > 30 µM. Danicopan did not inhibit OAT1.

An initial comparative analysis of the values obtained in the *in vitro* DDI assays and the free $C_{max}$ estimated for humans ($IC_{50}/C_{max}$, unbound) revealed no concern from these calculations. The Applicant examined then safety margins from repeat-dose *in vivo* toxicity studies in which hepatobiliary cholestasis was observed. In the 39-week dog toxicity study in Beagle dogs, the lowest dose with unequivocal hepatobiliary findings was 150 mg/kg/day (ACH-16-057). Mean $C_{max}$ values at this dose level on Day 273 (the final day of dosing) were 10100 ng/mL (17.4 µM) and 12300 ng/mL

(21.2 µM) for males and females, respectively. These $C_{max}$ values correspond to free danicopan concentrations of 1.84 µM to 4.47 µM (or 1840 nM to 4470 nM), calculated using free fractions of 10.6% to 21.1% in dog plasma. These free danicopan concentrations are 18× to 43× greater than the projected clinical $C_{max}$ of 104 nM free danicopan, calculated from a $C_{max}$ of 696 ng/mL (1.2 µM) at 200 mg tid in humans, and a free fraction of 8.7% at 1 µM. Accordingly, it was concluded that hepatobiliary findings in Beagle dogs do not indicate a DDI risk arising from hepatobiliary targets at therapeutic dose levels.

**Toxicology**

Results from repeat dose studies after a single dose were considered for acute toxicity effects.

Chronic repeat administration of danicopan to rats resulted in marked toxicity liver, adrenal glands and thyroid. The applicant considered the findings reported in the target organs of toxicity as an adaptive response to increased metabolic enzyme production, mainly in liver. However, taking into consideration the absence of hepatic metabolism in humans, the relevance of these findings in clinical practice is limited. Findings in adrenal glands (weight changes and histopathology analysis) were considered related to stress. This is not agreed, as microscopic findings related to adrenal glands in the 26-week repeat dose toxicity study in rats were reported in a dose dependent manner, and no findings were observed in the control group. Consequently, explanation provided by the applicant cannot be considered valid. In the case of thyroid (changes in TSH and T4), the mechanism proposed by the applicant is an increase in hormone catabolism that induces an additional release of thyroid stimulating hormones, followed by a trophic response of the thyroid gland. Further proliferation leading to adenomas and later carcinomas of the thyroid has been described by the applicant as rodent specific. In rats, exposure was generally higher in females compared to males.

Dog was selected as non-rodents species for the toxicology assessment of danicopan. Chronic administration (13-week and 39-week in duration) revealed liver as the main target organ of toxicity. In the case of dogs, hepatobiliary damage was markedly appreciated in these studies. In the 39-week toxicity study, danicopan at the dose of 150 mg/kg/day was not tolerated due to cholestatic liver injury. Hypertrophy/hyperplasia of the bile duct was observed in males at greater than or equal to 75 mg/kg/day. The Applicant argued that the isolated biliary findings at 75 mg/kg/day in the absence of corresponding clinical pathology correlates are not considered adverse and represent the study NOAEL. However, although the findings at this dose were less in severity and magnitude, the damage is clearly observed.

The different toxic profile of danicopan displayed in rats and dogs revealed a dissimilar mechanism of toxicity in both species. The latter one showed hepatobiliary damage as a consequence of a biliary tract dysfunction. In rats, liver damage was a consequence of metabolism, a mechanism of maintaining homeostasis after extended metabolic activity. Considering that danicopan is not pharmacologically active in rats, the toxic findings observed in this species cannot be considered as mechanism related. However, findings noted in dogs should be taken into account for clinical practice, given that a potential damage in humans cannot be ruled out.

In the 6-month toxicity study in rats (species not pharmacologically sensitive to danicopan), hypertrophy in liver, thyroid and adrenal gland was observed at doses of 1000 mg/kg/day (~26-fold above human exposure at 200 mg three times a day based on AUC).

Genotoxicity assessment of danicopan resulted in negative outcome in the Ames bacterial reverse mutation assay, *in vitro* micronucleus assay in human peripheral blood lymphocytes or in the *in vivo* micronucleus assay in rats. Potential carcinogenic effect was investigated in 6-month carcinogenicity study in TgRasH2 mice and in the 2-year rat carcinogenicity study, up to the dose of 1500 mg/Kg/day and 500 mg/Kg/day (250 mg/kg bid), respectively. Both studies were concluded as negative, although

rodent species are not considered pharmacologically relevant for danicopan. A higher incidence of endometrial epithelium neoplasms at the high dose of 500 mg/kg/day compared to control animals was observed although it is acknowledged that Han Wistar rat strain can have a high background incidence of endometrial carcinomas. In addition, the maximum dose tested has been discussed taking into account that the dose level of 1000 mg/Kg/day (BID 500 mg/Kg/day) was established by the applicant as NOAEL in the 6 month repeat dose toxicology study in rats. Section 5.3 of SmPC was updated accordingly.

Rabbit species was selected for DART studies, based on the absence of pharmacological activity of rats. In the fertility studies, reduced male and female reproductive performance was observed at 500 mg/kg/day, a dose associated at poor tolerability. NOAEL was established by the applicant at 250 mg/kg/day (7.2- and 8.8-fold above the human exposure), although systemic toxicity was noted at 125 mg/Kg/day (see section 5.3 of the SmPC).

EFD toxicity assessment was investigated in rabbits and rats, showing mortality and abortion at 1000 mg/Kg/day in rabbits. Information related to reproductive toxicity is included in the SmPC sections 4.6 and 5.3. As a precautionary measure, it is recommended to avoid the use of Voydeya during pregnancy. In the PPND study conducted in rabbits, NOAEL was established by the applicant at 250 mg/kg/day, the maximum dose tested in the study. A reduction of mean caudal epididymal sperm concentration in the F1 males was reported in the study report. This finding was noted in all dose groups (50, 125 and 250 mg/kg/day), being statistically significant in the low and mid dose groups (19, 20 and 18% respectively), although it was not observed in parallel with any alteration of reproductive performance or histopathological findings. The relevance of this finding in humans is unknown, however it has been reflected in section 5.3 of the SmpC.

Available pharmacodynamic/toxicological data in animals have shown excretion of danicopan/metabolites in milk. Danicopan was excreted into the milk of lactating rabbits following oral administration from lactation Day 4 to 10, with milk concentrations approximately 5 and 3.5 times higher compared to maternal plasma concentrations at 50 and 250 mg/kg/day, respectively (see section 5.3). A risk to the newborns/infants cannot be excluded. Voydeya should not be used during breast-feeding and breast-feeding should not be initiated until 3 days after treatment discontinuation. (see SmPC section 4.6).

The applicant presented the results of a Dose range finding Juvenile animal studie (DRF JAS) in dogs, although no definitive JAS has been performed. It is noted that changes observed in juvenile dogs were comparable to those observed in adult animals (hepatobiliary toxicity consisted in hypertrophy/hyperplasia of the bile ducts, usually accompanied by portal mixed cell infiltration, and acute degeneration/necrosis of bile ductal epithelium).

The interspecies comparison presented by the applicant showed lower safety margins in the case of dogs than in rats (danicopan is not pharmacologically relevant in rat species). Of note, rabbit species was selected as the primary non-clinical species for DART assessment, but omitted by the applicant in the interspecies comparison.

With regard to metabolites and impurities, Ames test for the metabolite 2-amino 6-bromopyridine, which is also an impurity (ACH-0144240), was presented in the section 3.2.r (regional section). Impurities were qualified in toxicology studies.

Although negative results were obtained in the *in vivo* phototoxicity study, the difference between human and rat species in terms of IC50 values (danicopan is not pharmacologically relevant in rats) should be taken into account for clinical practice.

Sections 4.6 and 5.3 of the SmPC have been adequately updated to reflect the information above.

Finally, danicopan PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, it is not expected to pose a risk to the environment.

***Assessment of paediatric data on non-clinical aspects***

Not applicable.

### 2.5.7. Conclusion on the non-clinical aspects

The non-clinical aspects of danicopan development are considered adequately discussed. All relevant information has been included in the SmPC sections 4.6 and 5.3.

## *2.6. Clinical aspects*

### 2.6.1. Introduction

***GCP aspects***

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

| Study Identifier: (Population) | Study Description | Number of Participants | Included in Pop-PK Analyses? | Dosing Duration[a] |
|---|---|---|---|---|
| ACH471-001 (Healthy adult participants) | Phase 1, randomized, double-blind, placebo-controlled, single-center SAD study to assess the safety, tolerability and PK of danicopan and to evaluate the relationship between danicopan PK and inhibition of AP activity (PK/PD). | Total: 44<br>Danicopan: 30<br>Placebo: 14 | Yes | Single-dose |
| ACH471-002 (Healthy adult participants) | Phase 1, randomized, double-blind (participant and Investigator blind, Sponsor open), placebo-controlled, single-center MAD study to assess safety, tolerability, PK, and PD of danicopan. | Total: 45<br>Danicopan: 31<br>Placebo: 14 | Yes | Cohorts 1 - 3: 14-day dosing period<br>Cohort 4: 7-day dosing period |
| ACH471-005 (Healthy adult male participants) | A Phase 1, open-label, single-center ADME study following a single 150 mg oral dose of $^{14}$C-danicopan containing approximately 100 µCi of $^{14}$C. | Total: 8<br>Danicopan: 8 | No[b] | Single-dose |
| ACH471-006 (Healthy adult participants) | A Phase 1, open-label, randomized, 3-period crossover study to determine the relative bioavailability, PK and safety of danicopan after administration of a tablet or softgel capsule versus a LFC in fasting and fed states. | Total: 26 | Yes | Single-dose |
| ACH471-009 (Healthy adult participants and participants with severe renal impairment) | A Phase 1, open-label, nonrandomized, multi-center, single-dose, parallel group study to evaluate the effect of renal impairment on safety, tolerability, and PK of danicopan. | Total: 16<br>Severe renal impairment: 8<br>Normal renal function: 8 | Yes | Single-dose |
| ACH471-010 (Healthy adult participants) | A Phase 1, open-label, single center, 3-part, fixed-sequence, 2-treatment, study to determine the potential drug interaction, safety, and tolerability between danicopan and midazolam, fexofenadine, and MMF. | Total: 35<br>Danicopan + midazolam: 11<br>Danicopan + fexofenadine: 12<br>Danicopan + MMF: 12 | Yes | Cohort 1: up to 4-day dosing period<br>Cohort 2: up to 6-day dosing period<br>Cohort 3: up to 6-day dosing period |

| Study Identifier: (Population) | Study Description | Number of Participants | Included in Pop-PK Analyses? | Dosing Duration[a] |
|---|---|---|---|---|
| ACH471-011 (Healthy adult participants) | A Phase 1, single-center, open-label, single-dose, non-randomized, fixed sequence study to evaluate the PK profile, safety, and tolerability of danicopan following administration of modified release prototype formulations. | Total: 14 | No[c] | Single-dose |
| ACH471-012 (Healthy adult participants and participants with moderate hepatic impairment) | A Phase 1, 2-part, open-label, multicenter, single-dose, parallel group study to determine the effect of hepatic impairment on the safety, tolerability, PK, and PD of danicopan. | Total: 16<br>Moderate hepatic impairment: 8<br>Normal hepatic function: 8 | Yes | Single-dose |
| ACH471-013 (Healthy adult participants) | A Phase 1 single ascending dose, randomized, double-blind, double dummy, placebo- and positive controlled, 2-arm, parallel study to evaluate the effect of danicopan on the QT interval. | Total: 33 | Yes | Single-dose |
| ACH471-014 (Healthy adult participants) | A Phase 1, 3-part (conducted concurrently), open-label, fixed-sequence, 2-period study to evaluate the potential drug interaction, and safety and tolerability between danicopan and cyclosporine, tacrolimus, antacids, and omeprazole. | Total: 72<br>Danicopan + cyclosporine: 14<br>Danicopan + tacrolimus: 28<br>Danicopan + antacids/omeprazole: 30 | Yes | Cohort 1: up to 7-day dosing period<br>Cohort 2: up to 10-day dosing period<br>Cohort 3: up to 8-day dosing period |
| ACH471-016 (Healthy young adult participants and healthy elderly participants) | A Phase 1 open-label, 2-part study to evaluate the effect of food and age on the PK, safety, and tolerability of danicopan.<br>Part 1 was a randomized, 2-sequence, 2-period crossover, single-dose definitive food-effect study, and Part 2 was a 1-period single-dose PK study. | Total: 25<br>Part 1: 18<br>Part 2: 7 | Yes | Single-dose |

| Study Identifier: (Population) | Study Description | Number of Participants | Included in Pop-PK Analyses? | Dosing Duration[a] |
|---|---|---|---|---|
| ACH471-017 (Healthy adult participants) | A Phase 1, 3-part, open-label, fixed-sequence, 2-period study to evaluate the potential drug interaction, and safety and tolerability between danicopan and warfarin, bupropion, and ethinyl estradiol/ norethindrone (oral contraceptive). | Total: 52<br>Danicopan + warfarin: 12<br>Danicopan + bupropion: 16<br>Danicopan + ethinyl estradiol/norethindrone: 24 | Yes | Cohort 1: up to 11-day dosing period<br>Cohort 2: up to 8-day dosing period<br>Cohort 3: up to 8-day dosing period |
| ALXN2040-HV-101 (Healthy adult participants of Japanese descent) | A Phase 1, open-label, randomized, single-dose, 3-period, three-treatment crossover study of danicopan to determine the safety, tolerability, and PK of danicopan after administration as an oral tablet in healthy participants of Japanese descent. | Total: 9 | Yes | Single-dose |
| ALXN2040-HV-119 (Healthy adult participants) | A Phase 1, 2-part, open-label, randomized, single-dose, 3-sequence, 3-period crossover, relative bioavailability, and food-effect study. | Total: 12 | No[c] | Single-dose |
| ACH471-100 (Untreated participants with PNH) | A Phase 2 open-label, multicenter, proof of concept, multiple-dose monotherapy study to assess the efficacy, safety and tolerability, PK, and PD of danicopan. | Total: 10 | Yes | Part 1: 28-day dosing period<br>Part 2: additional 56-day dosing period |
| ACH471-103 (Participants with PNH who completed Study ACH471-100) | A Phase 2 open-label, single-arm extension study to evaluate the efficacy and safety during long-term treatment with danicopan. | Total: 8 | No[d] | Long-term treatment |
| ACH471-101 (Participants with PNH who have an inadequate response to eculizumab monotherapy) | A Phase 2 multicenter, open-label, multiple-dose study to assess the efficacy, safety, and PK of danicopan as add-on treatment to eculizumab | Total: 12 (ongoing study) | Yes | Primary Evaluation Period: 24-week<br>Long-term Extension Period: ongoing (≥ 3years) |

| Study Identifier: (Population) | Study Description | Number of Participants | Included in Pop-PK Analyses? | Dosing Duration[a] |
|---|---|---|---|---|
| ALXN2040-PNH-301 (Participants with PNH who have clinically evident extravascular hemolysis while on concurrent treatment with C5 inhibitor, ravulizumab or eculizumab) | A Phase 3 multicenter, double-blind, study to assess the efficacy, safety, PK, PD, and immunogenicity of danicopan as add-on treatment to a C5 inhibitor (ravulizumab or eculizumab) | Total: N = 73 randomized and treated<br>PK Analysis Set: N = 71 (danicopan n = 48, placebo n = 23)<br>PD Analysis Set: N = 73 (danicopan n = 49, placebo n = 24) | Yes | Primary Evaluation Period: 24-week<br>Long-term Extension Period: ongoing (2 years) |

[a] Shown are the maximum dosing durations per study/cohort. Detailed dosing information per treatment regimen is provided in Section 2.
[b] Not included because this is an ADME study.
[c] Not included because formulations not pursued were evaluated.
[d] Not included because long-term extension study.
Abbreviations: ADME = absorption, distribution, metabolism, excretion; AP = alternative pathway; C5 = complement component 5; LFC = liquid-filled capsule; MAD = multiple ascending dose; MMF = mycophenolate mofetil; N = number of participants; PNH = paroxysmal nocturnal hemoglobinuria; PK = pharmacokinetics; PD = pharmacodynamics; SAD = single ascending dose

## 2.6.2. Clinical pharmacology

### *2.6.2.1. Pharmacokinetics*

**Analytical methods**

For the analysis of PK samples during the clinical development of danicopan, the following bionalytical methods were used:

- Determination of danicopan in plasma: Methods STM3030A, STM3030B and MWI4041
- Determination of danicopan in serum: Method STM3063
- Determination of danicopan in urine: Method STM3034

The bioanalytical methods STM3030A, STM3030B, STM3063 and STM3034 were validated by Pyxant Labs Inc. (Colorado Springs CO, USA).

For Study ACH471-011, danicopan plasma concentrations were determined using method MWI4041, which was validated by LGC Ltd (Cambridgeshire, UK).

Bioanalytical tests employed in the analysis of PD samples and biomarkers during the clinical development of danicopan were submitted, with the corresponding validation and bioanalytical reports (if available).

***Absorption***

Danicopan is absorbed after oral dosing, with mean time to maximum observed concentration occurring at about 3 hours post dose. An intravenous formulation of danicopan has not been developed. Therefore, the absolute bioavailability of danicopan in humans was not investigated.

- ***Bioequivalence***

The danicopan formulations used in the danicopan PNH programme are summarised by clinical study in Table 4. The planned commercial formulation of danicopan is the immediate-release tablet formulation used in pivotal Study ALXN2040-PNH-301. Danicopan drug product is formulated in 2 strengths, 50 mg and 100 mg tablets, manufactured using a common blend.

**Table 4: Danicopan Formulations Used in Clinical Studies**

| Formulation | Strength | Clinical Studies |
|---|---|---|
| LFC | 75 mg | ACH471-002 |
| | 100 mg | ACH471-002 and ACH471-006 |
| | 200 mg | ACH471-001 |
| | 600 mg | ACH471-001 |
| | 1200 mg | ACH471-001 |
| Softgel capsule | 100 mg | ACH471-006 |
| IR tablet | 50 mg | ACH471-010, ACH471-100, ACH471-101, ACH471-103, and ALXN2040-PNH-301 |
| | 75 mg | ACH471-100, ACH471-101, and ACH471-103 |
| | 100 mg | ACH471-006, ACH471-009, ACH471-010, ACH471-012, ACH471-013, ACH471-014, ACH471-016, ACH471-017, ALXN2040-HV-101, ALXN2040-HV-119, ACH471-100, ACH471-103, ACH471-101, and ALXN2040-PNH-301 |
| MR Prototype 1 tablet | 400 mg | ACH471-011 |
| MR Prototype 2 tablet | 400 mg | ACH471-011 |
| MR Prototype 3 tablet | 200 mg | ACH471-011 |
| Prototype PIC 1 | 200 mg | ALXN2040-HV-119 |
| Prototype PIC 2 | 200 mg | ALXN2040-HV-119 |

Abbreviations: IR = immediate release; LFC = liquid-filled capsule; MR = modified release; PIC = powder in capsule

Source: ACH471-001 CSR Section 9.4.1; ACH471-002 CSR Section 9.6.4; ACH471-006 CSR Section 9.8.1; ACH471-009 CSR Section 9.4.1; ACH471-010 CSR Section 9.4.1; ACH471-011 CSR Section 9.4.1; ACH471-012 CSR Section 9.4.1; ACH471-013 CSR Section 9.4.1; ACH471-014 CSR Section 9.4.2; ACH471-016 CSR Section 3.4.1; ACH471-017 CSR Section 9.4.1; ACH471-100 CSR Section 9.4.2; ACH471-101 CSR Section 3.4.1; ACH471-103 CSR Section 3.4.1; ALXN2040-HV-101 CSR Section 3.4.1; ALXN2040-HV-119 CSR Section 3.4.1; and ALXN2040-PNH-301 CSR Section 3.4.1

No formal bioequivalence studies were conducted since the to-be-marketed formulation was tested in the phase III clinical study.

- ***Influence of food***

**Study ACH471-016** Following administration of danicopan under fed (high-fat meal) conditions (Treatment A), geometric mean AUC0-t, AUC0-inf, and $C_{max}$ were 3496 ng*hr/mL, 3501 ng*hr/mL, and 825.9 ng/mL, respectively. Following administration of danicopan under fasted conditions (Treatment B), geometric mean AUC0-t, AUC0-inf, and $C_{max}$ were 2698 ng*hr/mL, 2711 ng*hr/mL, and 426.4 ng/mL, respectively. Mean apparent total clearance (CL/F) was lower following administration of danicopan under fed conditions (59.20 L/hr) compared to under fasted conditions (76.42 L/hr). Similarly, mean apparent volume of distribution (Vz/F) reduced to 635.6 L following dosing under fed conditions compared to 1020 L under fasted conditions. This difference is likely due to an increase in the bioavailable fraction (F) when danicopan is administered under fed conditions. There was no marked difference in elimination t½ following administration of danicopan under fed conditions with mean values of 7.249 hours compared to 8.757 hours under fasted conditions.

Following a single dose of danicopan administered with a high-fat/high calorie meal, peak concentrations, based on geometric mean $C_{max}$, were approximately 93% higher compared to danicopan administered under fasted state. A lesser increase of approximately 25% was observed in overall exposure (geometric least-squares mean AUC0-t or AUC0-inf) under fed as compared to in the fasted state. The increase in exposure is likely due to increased solubility of danicopan when

administered with a high-fat/high-calorie meal. Of note, the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) (high-fat meal/fasted) for AUCs and $C_{max}$ were not contained within the no-effect boundary of 80.00 to 125.00%. Food had no significant effect on danicopan median $T_{max}$ with values of approximately 3.0 and 2.5 hours when administered under fed and fasted conditions, respectively. However, individual $T_{max}$ values were variable with values ranging from 1.0 to 8.0 hours. There was no marked difference in elimination t½ with mean values of approximately 7 to 9 hours following administration of danicopan under fed and fasted conditions, respectively. Intra-participant CV% values were approximately 11% for the AUCs and 28% for $C_{max}$. Inter-participant variability in overall exposure (AUC) was comparable between fed (high-fat meal) and fasted conditions, with geometric CV% values ranging between 27.6% and 28.7% over both treatments. Inter-participant variability in peak exposure ($C_{max}$) was reduced under fed (high-fat meal) (37.4%) compared to fasted (50.4%) conditions.

***Distribution***

**Study ACH471-005** In the human 14C ADME study, plasma danicopan concentration appeared to decline in a biphasic manner after $T_{max}$. The ratio of mean values for AUC0-inf determined based on plasma and whole blood radioactivity was 0.545; this result suggests very limited, if any, partitioning of [14C] danicopan-derived radioactivity into blood cells.

***Elimination***

**Study ACH471-005** Cumulative results for recovery of radioactivity at 216 hours after dosing were as follows (all percentages were calculated relative to the total administered dose of 14C radiolabel):

- The mean recovery in total excreta (ie, urine + feces together) was 94.0% (range: 91.0% to 97.2%).
- The primary route for elimination of 14C radiolabel was fecal, as the mean recovery specifically in feces was 69.2%. Most of the observed fecal radioactivity (40.3% of the total 14C radiolabel administered) was recovered within 48 hours after dosing.
- The secondary route for elimination of 14C radiolabel was urinary, as the mean recovery specifically in urine was 24.8%. Most of the observed urinary radioactivity (14.1% of the total 14C radiolabel administered) was recovered within 4 hours after dosing.

14C-danicopan was extensively metabolised (96%) after oral administration via oxidation, reduction, and hydrolysis. Thirteen metabolites were tentatively identified, in addition to ACH-0145071, ACH-0145072, ACH-0144240, ACH-0144709, ACH-0145069, and ACH-0145070 (see table below).

**Table 5: Summary of Metabolites Identified in Human Plasma, Urine, and Feces**

| Metabolite Designation | Retention Time (Minutes) | Proposed Identification | Matrix | | |
|---|---|---|---|---|---|
| | | | Plasma[a] | Urine[b] | Feces[b] |
| M1 | 11.00 | Dioxy-ACH-0145071/ACH-0145072 | | | 1.28 |
| M2 | 12.25-12.50 | Pyrrolidine ring-opened-ACH-0145071/ACH-0145072 | | 0.197 | 0.953 |
| M3 | 13.25 | Des-[pyrrolidine carboxylic acid] ACH-0145071/ACH-0145072 | | | 0.979 |
| M4 | 13.75 | Dioxy-ACH-0144709 | | | 1.09 |
| ACH-0145071/ACH-0145072 (M5) | 15.25-15.50 | ACH-0145071/ACH-0145072 | 10.97 | 6.96 | 10.8 |
| M6 | 17.50-17.75 | Pyrrolilidine ring-opened-ACH-0144709 | | | 1.68 |
| M7 | 18.25-18.50 | Des-[pyrrolidine carboxylic acid] ACH-0144709 | | 0.160 | 2.50 |
| ACH-0144240 (M17) | 20.82[c]-20.86[c] | ACH-0144240 | [d] | [d] | [d] |
| ACH-0144709 (M8) | 23.50-23.75 | ACH-0144709 | 52.53 | 14.4 | 32.8 |
| M9 | 32.00 | Dioxy-ACH-0145069/ACH-0145070 | 0.63 | 0.219 | 1.23 |
| M10 | 40.50-40.75 | Dioxy-ACH-0144471 | 1.79 | 0.243 | 2.12 |
| M11 | 44.25 | Oxy-ACH-0144471-1 | | | 1.86 |
| M12 | 45.00 | Oxy-ACH-0145069/ACH-0145070 | 1.05 | | |
| ACH-0145069/ACH-0145070 (M13) | 46.00-46.25 | ACH-0145069/ACH-0145070 | 2.64 | 0.427 | 0.529 |
| M14 | 48.25 | Oxy-ACH-0144471-2 | 1.79 | | |
| M15 | 49.25 | Pyrrolidine ring-opened-ACH-0144471 | | | 0.308 |
| M16 | 56.50 | Oxy-ACH-0144471-3 | 4.64 | | |
| ACH-0144471 | 58.25 | ACH-0144471 | 22.89 | 0.481 | 3.57 |
| Total | | | 98.9 | 23.0 | 61.7 |

Notes: Retention time ranges are from profiling analyses of all matrices.

a % of the total radioactivity $AUC_{0.5-4h}$
b % of the dose.
c Retention time for MS only.
d M17 does not contain the radiolabel and was detected by MS only.

***Dose proportionality and time dependencies***

**Study ACH471-001** Subjects in Groups 1 (200 mg fasted), Group 2 (600 mg fasted) and Group 3 (1200 mg fasted) were included in the dose proportionality analysis.

Based on the statistical analysis to assess dose proportionality, the increase for both $C_{max}$ and AUC0-inf appeared to be less than dose proportional over the dose range tested (200 to 1200 mg) in the fasted state based on the estimated proportionality co-efficient (B) of 0.64 and 0.82, respectively (Tables below). The 90% CIs did not include 1 and were both less than 1, which tentatively conclude less than dose-proportionality. The small sample size for each dose may have contributed to this result.

**Table 6: Dose proportionality (power model) assessment of plasma ACH-0144471 $C_{max}$**

| Parameter | Estimate | Lower 90% CI | Upper 90% CI |
|---|---|---|---|
| Ln(A) | 3.47 | 2.29 | 4.64 |
| B | 0.64 | 0.46 | 0.83 |

Subjects in Groups 1 (200 mg fasted), Group 2 (600 mg fasted) and Group 3 (1200 mg fasted) were included in the dose proportionality analysis.
Ln ($C_{max}$) = ln (A) + B* ln (dose), where ln (A) is a constant, B is the proportionality co-efficient.
CI, confidence interval; $C_{max}$, maximum plasma concentration; Ln, natural log; %, percent
Source: Table 14.2.3-2

**Table 7: Dose Proportionality (Power Model) Assessment of Plasma ACH-0144471 AUC0-inf**

| Parameter | Estimate | Lower 90% CI | Upper 90% CI |
|---|---|---|---|
| Ln(A) | 3.65 | 2.85 | 4.45 |
| B | 0.82 | 0.69 | 0.95 |

Subjects in Groups 1 (200 mg fasted), Group 2 (600 mg fasted) and Group 3 (1200 mg fasted) were included in the dose proportionality analysis.
Ln ($C_{0\text{-inf}}$) = ln (A) + B* ln (dose), where A is a constant, B is the proportionality co-efficient.
$AUC_{0\text{-inf}}$, area under the concentration-versus-time curve extrapolated to infinity; CI, confidence interval; Ln, natural log; %, percent
Source: Table 14.2.3-3

**Study ACH471-002** In Study ACH471-002, multiple oral doses of danicopan as a LFC were evaluated under fasting conditions: 200 mg bid, 500 mg bid, 800 mg bid, and 75 mg tid.

Dose-proportionality of ACH-0144471 multiple-dose PK was explored by comparing log transformed $C_{max}$ and AUCtau values on Day 14 after first dose using the power model. Subjects in Cohort 1, Cohort 2, and Cohort 3 were included in the dose proportionality analysis.

Based on the statistical analysis to assess dose proportionality, the increase for both $C_{max}$ and AUCtau appeared to be dose proportional over the dose range tested (200 to 800 mg BID) based on the estimated proportionality coefficient (90% CI) of 0.96 (0.74, 1.18) and 1.04 (0.87, 1.21), respectively (Tables below). The 90% CI for both variables included 1, indicating dose-proportional PK of ACH-0144471 in the dose range tested.

**Table 8: Dose Proportionality (Power Model) Assessment of Plasma ACH-0144471 $C_{max}$ for Day 14 (Cohort 1-3)**

| Coefficient/Constant | Estimate | Lower 90% CI | Upper 90% CI |
|---|---|---|---|
| Ln(A) | 1.65 | 0.33 | 2.97 |
| B | 0.96 | 0.74 | 1.18 |

Ln ($C_{max}$) = ln (A) + B* ln (dose), where ln (A) is a constant, B is the proportionality coefficient.
Abbreviations: $AUC_{tau}$, area under the plasma concentration-time curve from time of administration to the end of the dosing interval; CI, confidence interval; $C_{max}$, maximum plasma concentration; Ln, natural log; %, percent
Source: Table 14.2.7-1

**Table 9: Dose Proportionality (Power Model) Assessment of Plasma ACH-0144471 AUCtau for Day 14 (Cohort 1-3)**

| Coefficient/Constant | Estimate | Lower 90% CI | Upper 90% CI |
|---|---|---|---|
| Ln(A) | 2.20 | 1.16 | 3.24 |
| B | 1.04 | 0.87 | 1.21 |

Ln ($C_{0\text{-inf}}$) = ln (A) + B* ln (dose), where A is a constant, B is the proportionality coefficient.
Abbreviations: $AUC_{tau}$, area under the plasma concentration-time curve from time of administration to the end of the dosing interval; CI, confidence interval; Ln, natural log; %, percent
Source: Table 14.2.8-1

***Time dependency***

The accumulation ratios for $C_{max}$, calculated as the ratios of $C_{max}$ at steady state (Day 7 and Day 14) to $C_{max}$ on Day 1 and for AUCtau, calculated as the ratios of AUCtau at steady state (Day 7 and Day 14) to AUCtau on Day 1 were expressed as geometric mean and %CV geometric mean. No accumulation of danicopan was observed in Cohort 1 and Cohort 4 as indicated by the observed geometric means of accumulation ratios, which ranged from 0.92 to 1.03. In Cohorts 2 and 3, when comparing the exposures ($C_{max}$ and AUCtau) between Day 7, Day 14, and Day 1, danicopan did not accumulate to a great extent as indicated by the observed geometric means of accumulation ratios, which are ranging from 1.16 to 1.77 for $C_{max}$ and 1.24 to 1.53 for AUCtau.

**Table 10: Accumulation Ratio for $C_{max}$ for Days 7 and 14 Following Danicopan in Healthy Adult Participants (Study ACH471-002)**

| Statistic | Cohort 1 (200 mg bid) | | Cohort 2 (500 mg bid) | | Cohort 3 (800 mg bid) | | Cohort 4 (75 mg tid) |
|---|---|---|---|---|---|---|---|
| | Day 7 | Day 14 | Day 7 | Day 14 | Day 7 | Day 14 | Day 7 |
| N | 8 | 8 | 7 | 7 | 8 | 8 | 8 |
| Geometric mean | 1.004 | 1.006 | 1.158 | 1.230 | 1.293 | 1.768 | 0.9162 |
| Geometric mean %CV | 24 | 40 | 18 | 27 | 22 | 34 | 21 |

Note: Accumulation Ratio = $C_{max,Day\ 7\ or\ 14}/C_{max,Day\ 1}$
Abbreviations: bid = 2 times a day; $C_{max}$ = maximum observed concentration; CV = coefficient of variation; tid = 3 times a day
Source: ACH471-002 CSR Table 14.2.3-1 and Table 14.2.3-2

**Table 11: Accumulation Ratio for AUCtau for Days 7 and 14 Following Danicopan in Healthy Adult Participants (Study ACH471-002)**

| Statistic | Cohort 1 (200 mg bid) | | Cohort 2 (500 mg bid) | | Cohort 3 (800 mg bid) | | Cohort 4 (75 mg tid) |
|---|---|---|---|---|---|---|---|
| | Day 7 | Day 14 | Day 7 | Day 14 | Day 7 | Day 14 | Day 7 |
| N | 8 | 8 | 7 | 7 | 8 | 8 | 8 |
| Geometric mean | 0.9995 | 1.032 | 1.293 | 1.237 | 1.264 | 1.527 | 1.002 |
| Geometric mean %CV | 15 | 16 | 20 | 17 | 17 | 20 | 12 |

Note: Accumulation Ratio = $AUC_{tau,Day\ 7\ or\ 14}/AUC_{tau,Day\ 1}$
Abbreviations: $AUC_{tau}$ = area under the concentration-time curve from time of administration to the end of the dosing interval; bid = 2 times a day; CV = coefficient of variation; tid = 3 times a day
Source: ACH471-002 CSR Table 14.2.4-1 and Table 14.2.4-2

**Pharmacokinetics in target population**

**Population pharmacokinetics**

The PPK data set included 7044 post-dose PK samples, including 6395 PK samples from 316 healthy subjects and 649 PK samples from 22 patients with PNH. Of these PK samples, 248 (4%) were BLQ, thus were excluded in the modelling analysis. Two (2) outliers were also excluded. The modelling analysis included 6757 danicopan PK samples from 338 subjects.

Base PopPK model

Model development was guided by evaluation of exploratory graphical analysis. A two compartment model with linear elimination was considered the starting model. Absorption was described by a zero-order release followed by first order absorption into the central compartment, with separate parameters estimated for LFC and tablet formulations.

The model was parameterised in terms of apparent clearance (CL/F), apparent volume of the central compartment (Vc/F), apparent volume of the peripheral compartment (Vp/F), apparent intercompartmental clearance (Q/F), the first order absorption rate constant (Ka), the duration of the zero-order release (D1) and the relative bioavailability referenced to the tablet formulation, standard meal and 200 mg dose (F).

Based on exploratory plots, F was modelled to increase for LFC relative to the tablet formulation and decrease with dose. The effect of a food (fasted and high fat meal relative to a standard meal) was modelled on F and D1. In addition, the effect of body weight on danicopan PK, was modelled on the volume terms (Vc/F and Vp/F) and on the clearance terms (CL/F and Q/F).

Final PPK Model

The final PK parameter and covariate relationship are given as:

$$CL/F_i = 81.3 \times (\frac{WT_i}{75})^{0.663} \times [1 - 0.218 \times (if\ Female)] \times [1 - 0.427 \times (if\ severe\ RI)]$$

$$Vc/F_i = 173 \times (\frac{WT_i}{75})^{0.872}$$

$$Q/F_i = 34.1 \times (\frac{WT_i}{75})^{0.663}$$

$$Vp/F_i = 232 \times (\frac{WT_i}{75})^{0.872}$$

$$Ka_i = (1.02(if\ Tablet) + 0.741\ (if\ LFC)) \times\times (1 + 6.97\ (\text{if FAST}))$$

$$D_{1i} = (3.14\ (if\ Tablet) + 1.51 \times (if\ LFC)) \times e^{0.123\ (if\ FAST)}$$

$$F_i = 1 \times 0.741(if\ LFC) \times (\frac{Dose_i}{200})^{-0.235} \times e^{-0.136\ (if\ FAST)} \times e^{0.108\ (if\ HIFAT)}$$

The final PPK model parameter estimates are presented in Table 12.

**Table 12: Population Parameter Estimates for the Final PPK Model**

| Parameter | Unit | Estimate | RSE (%) | Shrinkage (%) |
|---|---|---|---|---|
| CL/F | L/hr | 81.3 | 2.3 | |
| Vc/F | L | 173 | 6.2 | |
| Q/F | L/hr | 34.1 | 2.48 | |
| Vp/F | L | 232 | 4.37 | |
| Ka (tablet) | 1/hr | 1.02 | 12.4 | |
| $D_1$ (tablet) | hr | 3.14 | 1.89 | |
| F of LFC relative to tablet | | 1.28 | 2.06 | |
| Dose on F | | -0.235 | 5.65 | |
| Ka (LF) | 1/hr | 0.741 | 119 | |
| $D_1$ (LFC) | hr | 1.51 | 2.9 | |
| Weight exponent on Vc/F and Vp/F | | 0.872 | 17.7 | |
| Weight exponent on CL/F and Q/F | | 0.663 | 11.2 | |
| Fasted on F | | -0.136 | 16.2 | |
| High fat meal on F | | 0.108 | 25.5 | |
| Fasted on $D_1$ | | 0.123 | 18 | |
| RI on CL/F | | -0.427 | 13.3 | |
| Female sex on CL/F | | -0.218 | 12.2 | |
| Fasted on Ka | | 6.97 | 16.3 | |
| **IIV (% BSV)** | | | | |
| $\omega^2$ CL/F | | 0.064 (25.3 %) | 7.99 | 6.8 |
| $\omega$_CL/F x $\omega$_Vc/F | | 0.0792 | 19.6 | - |
| $\omega^2$_Vc/F | | 0.432 (65.7 %) | 14.2 | 23.6 |
| $\omega^2$_Vp/F | | 0.152 (39.0 %) | 14.9 | 36.5 |
| $\omega^2$_Ka | | 0.911 (95.4 %) | 15.5 | 26.0 |
| **Residual Error** | | | | |
| Proportional | % | 44.6 | 0.642 | 4.1 |
| Additive | ng/mL | 0.229 | 6.68 | 4.1 |

Abbreviations: PPK = population pharmacokinetics; BSV= between-subject variability; CL/F= apparent clearance; CV = coefficient of variation; $D_1$ = duration of zero order release; F= relative bioavailability with reference to the tablet formulation, standard meal and 200 mg dose; IIV = interindividual variability; Ka = first order absorption rate; LFC = liquid-filled capsule; Q/F = apparent intercompartmental clearance; RI = severe renal impairment; RSE = relative standard error; Vc/F = apparent volume of the central compartment; Vp/F = apparent volume of the peripheral compartment.

Notes: IIV was reported as variance ($\omega^2$) and % between subject variability (BSV, $\omega$ x 100%); RSE calculated as standard error/estimate x 100%. Median elimination half-life was calculated to be 7.3 hr (4.5 to 13.6, 2.5 to 97.5%ile of the population).

Source: final.pk.model.r

PK model update

The previous danicopan PPK model was used as a starting point of the current model development.

The PPK data set contains 7491 post-dose PK samples from 407 subjects in 14 clinical studies, including 440 PK samples from 69 adult patients with PNH in study ALXN2040-PNH-301.

Base model of the current analysis included the following covariates identified in the previous population PK analysis as reported in the pooled Phase 1 and 2 population PK report: different Ka and D1 for the LFC formulation; fasted on F1, D1 and Ka; high fat meal on F1; RI on CL/F; and WT on CL/F, Vc/F, Q/F and Vp/F. Sex Female was also a significant covariate in the previous model, nevertheless, it was re-evaluated in the current covariate analysis along with many other

disease-related and ethnic/region covariates which includes country (Japan vs non-Japan) and region (East Asia vs non-East Asia).

Covariates were evaluated using a forward additional following by backward elimination steps. Significant (p value < 0.01 in likelihood ratio test) covariates identified in the forward addition steps included: sex on CL/F, C5 inhibitors on CL/F, East Asia region on Vc/F and Japan country on CL/F. In the following backward elimination step using a more stringent criteria (p value < 0.001 in likelihood ratio test), C5 inhibitors on CL/F, East Asia on Vc/F and Japan on CL/F were dropped off from the model, while sex on CL/F was retained in the final model. The final model in the current analysis had similar covariates as previous analysis.

Final PPK Model

The final PK parameter and covariate relationship are given as:

$$CL/F_i = 79.5 \times (\frac{WT_i}{75})^{0.665} \times [1 - 0.227 \times (if\ Female)] \times [1 - 0.413 \times (if\ severe\ RI)] \times \exp(ETA1)$$

$$Vc/F_i = 165 \times (\frac{WT_i}{75})^{0.932} \times \exp(ETA2)$$

$$Q/F_i = 34.1 \times (\frac{WT_i}{75})^{0.663}$$

$$Vp/F_i = 232 \times (\frac{WT_i}{75})^{0.932} \times \exp(ETA3)$$

$$Ka_i = [1.11(if\ Tablet) + 0.739\ (if\ LFC) + 7.15\ (\text{if FAST})] \times \exp(ETA4)$$

$$D_{1i} = [3.17\ (if\ Tablet) + 1.54(if\ LFC)] \times e^{0.107(if\ FAST)} \times \exp(ETA5)$$

$$F_i = 1 \times 1.30(if\ LFC) \times (\frac{Dose_i}{200})^{-0.242} \times e^{-0.161\ (if\ FAST)} \times e^{0.0877\ (if\ HIFAT)}$$

The final PPK model parameter estimates are presented in **Table 13**.

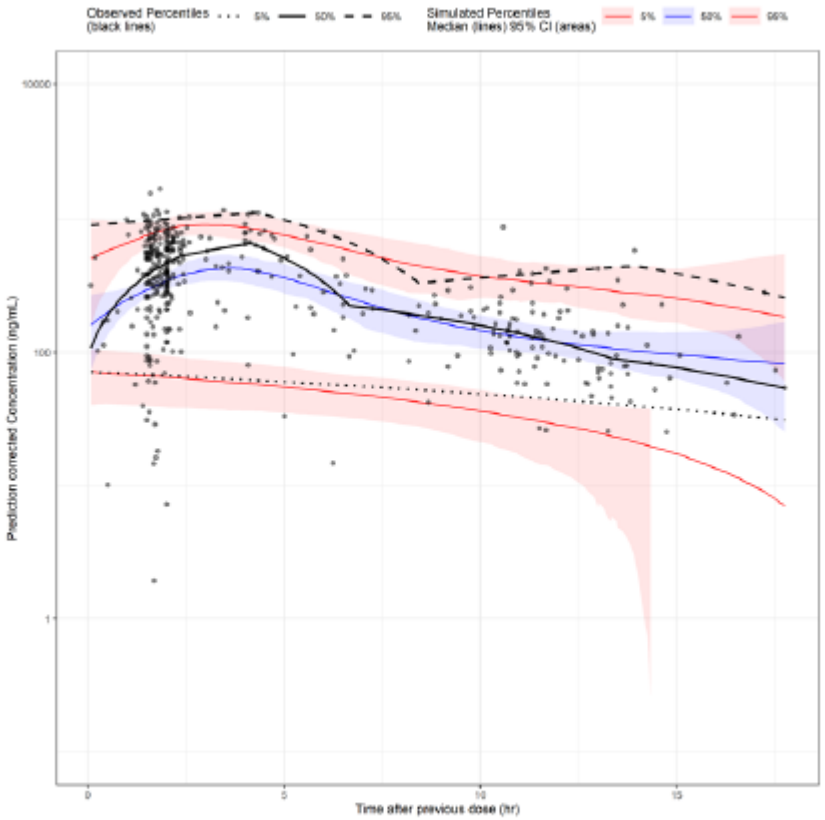
**Table 13: Population Parameter Estimates for the Final PPK Model**

| Parameter | Unit | Estimate | RSE (%) | Shrinkage (%) |
|---|---|---|---|---|
| CL/F | L/hr | 79.5 | 1.96 | |
| Vc/F | L | 165 | 4.72 | |
| Q/F | L/hr | 34.1 | 3.31 | |
| Vp/F | L | 232 | 3.91 | |
| Ka (tablet) | 1/hr | 1.11 | 7.62 | |
| $D_1$ (tablet) | hr | 3.17 | 1.94 | |
| F of LFC relative to tablet | | 1.3 | 3.13 | |
| Dose on F | | -0.242 | 8.06 | |
| Ka (LFC) | 1/hr | 0.739 | 30.3 | |
| $D_1$ (LFC) | hr | 1.54 | 3.96 | |
| Weight exponent on Vc/F and Vp/F | | 0.932 | 15.2 | |
| Weight exponent on CL/F and Q/F | | 0.665 | 12 | |
| Fasted on F | | -0.161 | 17.5 | |
| High fat meal on F | | 0.0877 | 41.2 | |
| Fasted on $D_1$ | | 0.107 | 26.0 | |
| RI on CL/F | | -0.413 | 13.0 | |
| Female sex on CL/F | | -0.227 | 10.8 | |
| Fasted on Ka | | 7.15 | 19.8 | |
| IIV (% BSV) | | | | |
| $\omega^2$ CL/F | | 0.0697 (26.4%) | 9.57 | 8.0 |
| $\omega$ CL/F x $\omega$ Vc/F | | 0.0897 | 16.2 | - |
| $\omega^2$ Vc/F | | 0.442 (66.5%) | 11.6 | 24.9 |
| $\omega^2$ Vp/F | | 0.152 (39.0%) | 13.1 | 41.2 |
| $\omega^2$ Ka | | 0.936 (96.7%) | 12.7 | 28.7 |
| **Residual Error** | | | | |
| Proportional | % | 44.7 | 1.06 | 4.4 |
| Additive | ng/mL | 0.23 | 12.8 | 4.4 |

Abbreviations: BSV= between-subject variability; CL/F= apparent clearance; $D_1$ = duration of zero order release; F= relative bioavailability with reference to the tablet formulation, standard meal and 200 mg dose; IIV = interindividual variability; Ka = first order absorption rate; LFC = liquid-filled capsule; PPK = population pharmacokinetics; Q/F = apparent inter-compartment clearance; RI = severe renal impairment; RSE = relative standard error; Vc/F = apparent volume of the central compartment; Vp/F = apparent volume of the peripheral compartment.

Notes: IIV was reported as variance ($\omega^2$) and % between subject variability (BSV, $\omega$ x 100%); RSE calculated as standard error/estimate x 100%.

Source: pk.final.model.r




Abbreviations: VPC = visual predictive check; PPK = population pharmacokinetics.
Source: pk.vpc.r

**Figure 3: pcVPC for Final PPK Model of Study ALXN2040-PNH-301**

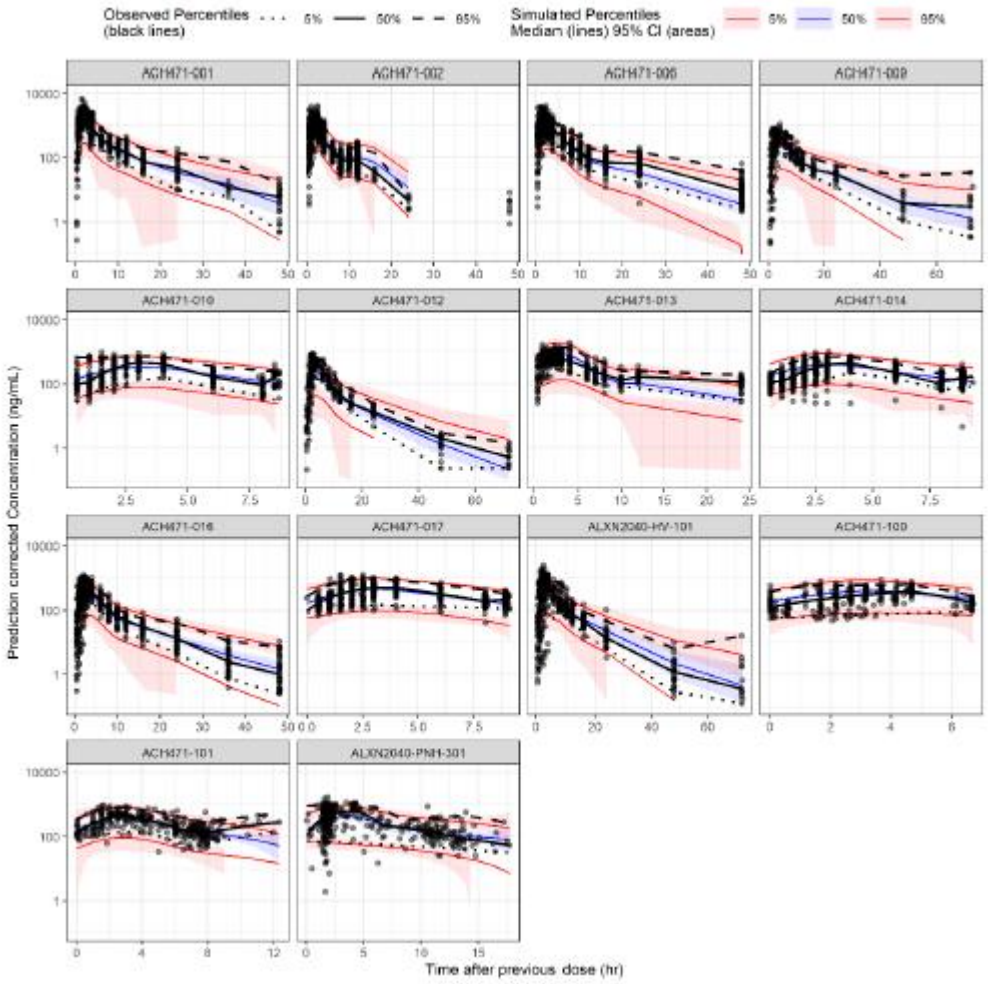
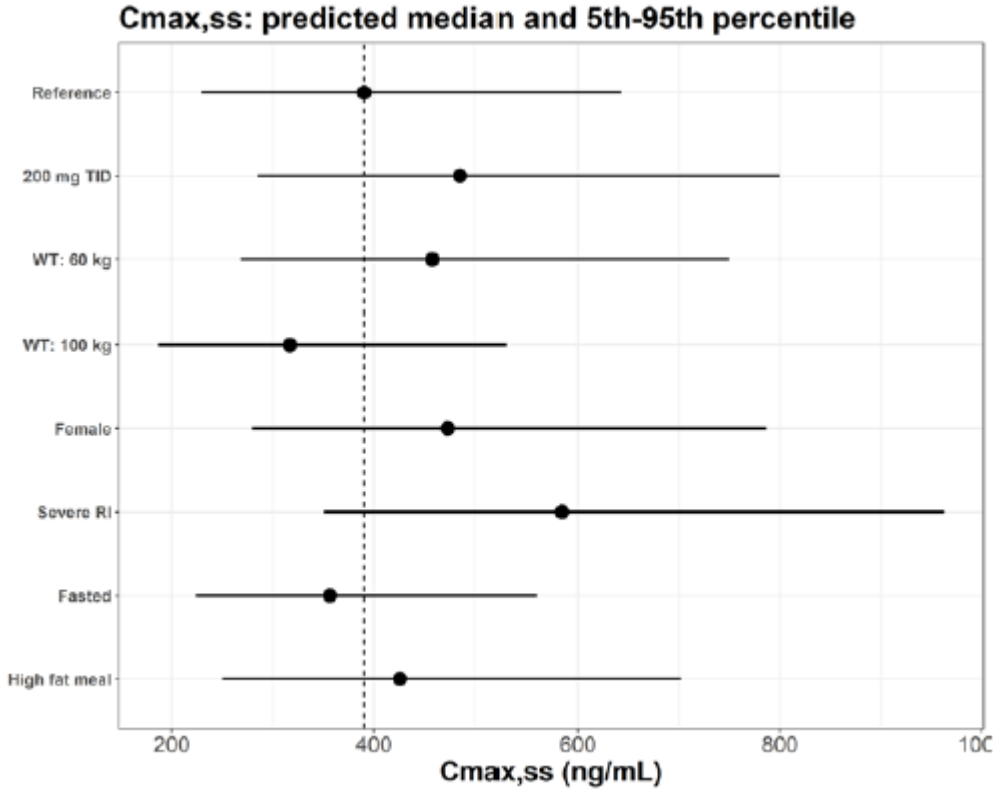
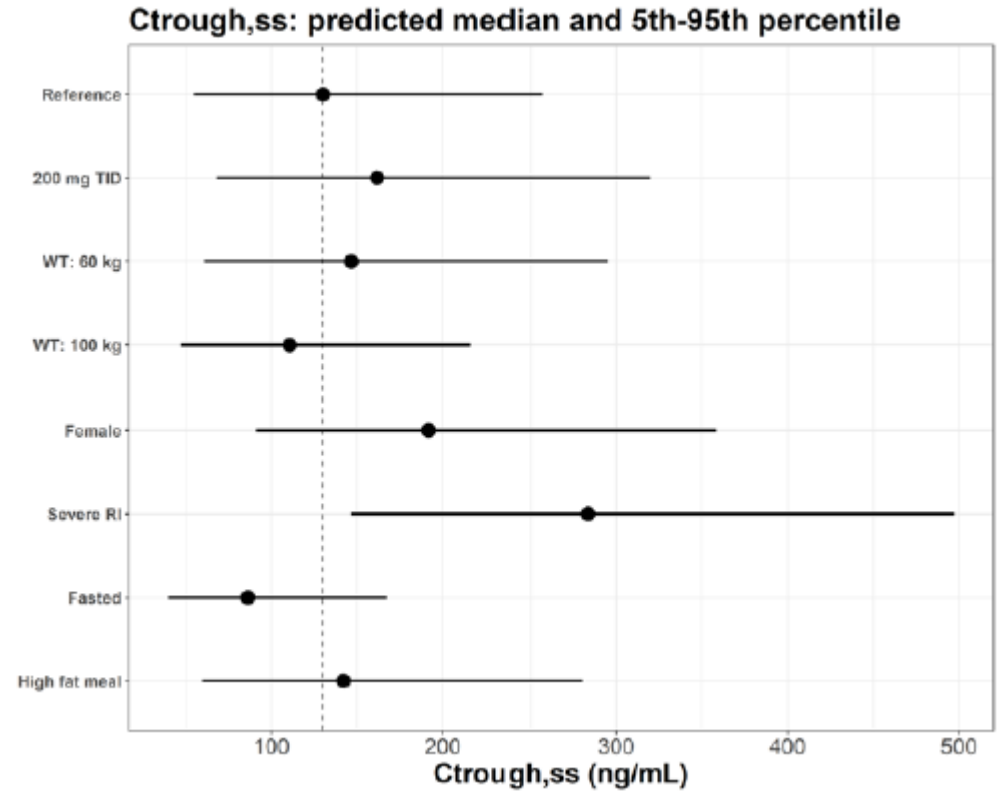
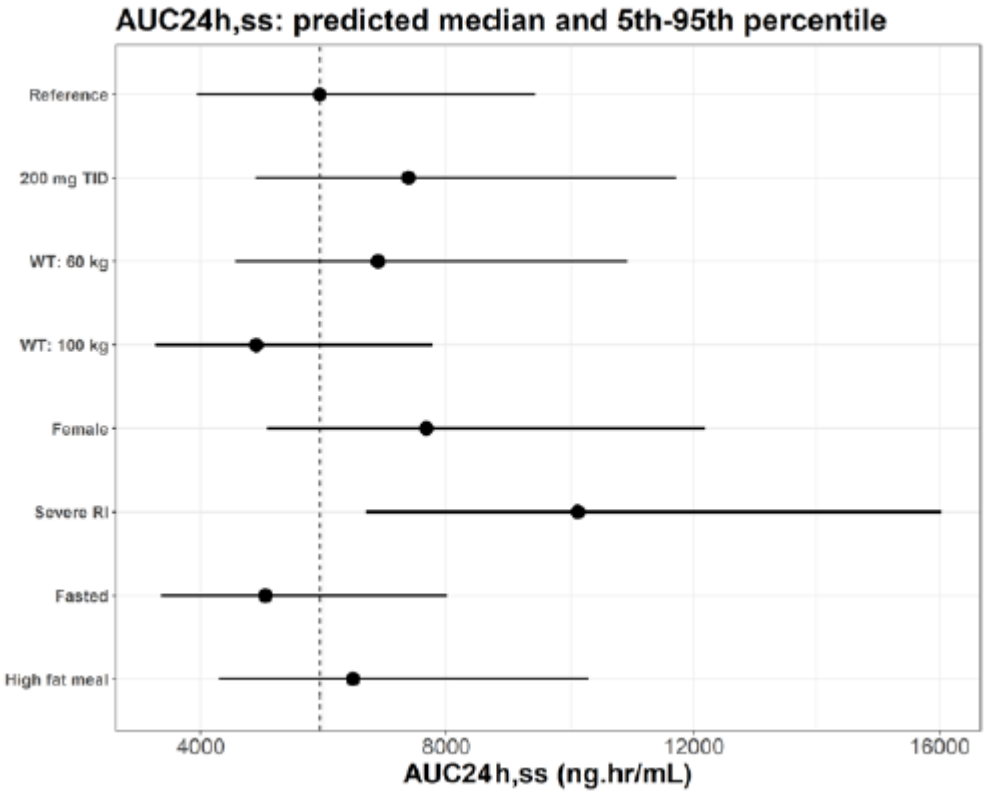



**Figure 4: pcVPC for Final PPK Model of for by Study**

The impact of covariates included in the final PPK model was evaluated using forest plots of relative changes in steady state exposure assuming a 150 mg TID regimen (unless otherwise noted) when covariates were varied one at a time (i.e., univariate analysis) (Figure below). A statistical summary of the simulated exposures is provided in Table 14.


Cmax,ss: predicted median and 5th-95th percentile
Reference
200 mg TID
WT: 60 kg
WT: 100 kg
Female
Severe RI
Fasted
High fat meal
200
400
600
800
Cmax,ss (ng/mL)


Ctrough,ss: predicted median and 5th-95th percentile
Reference
200 mg TID
WT: 60 kg
WT: 100 kg
Female
Severe RI
Fasted
High fat meal
100
200
300
400
500
Ctrough,ss (ng/mL)




Abbreviations: AUC = area under the concentration-time curve; TID = three times daily; Cmax = maximum concentration; Ctrough = trough concentration; RI = renal impairment; WT = body weight.

Note: Vertical dashed line indicates the steady-state exposure for a typical subject (reference) treated with danicopan 150 mg TID. Error bars indicate the 5$^{th}$ to 95$^{th}$ percentile of the exposure of 1000 simulated subjects based on the typical PK parameters, between-subject variability, and the dose or covariate values. A typical patient is defined as a male with body weight of 75 kg, normal renal function and administered 150 mg TID tablet with a standard meal. "Severe RI" was defined per ACH471-009 study reported "severe renal impairment" group.

Source: pk.forestplot.r

**Figure 5: Sensitivity of Danicopan Steady State Exposures to Covariates and Dose**

**Table 14: Impact of Covariates and Dose on Steady State Danicopan Exposure**

| Exposure Metric | Scenario | Median [5th and 95th Percentiles] | Mean (SD) | Fold/Ref[1] |
|---|---|---|---|---|
| Cmax,ss (ng/mL) | Reference | 390 [229 – 643] | 406 (131) | 1 |
| | 200 mg TID | 485 [285 – 800] | 505 (163) | 1.24 |
| | WT: 60 kg | 458 [268 – 750] | 476 (153) | 1.17 |
| | WT: 100 kg | 317 [186 – 529] | 331 (107) | 0.812 |
| | Female | 473 [279 – 786] | 494 (158) | 1.21 |
| | Severe RI | 584 [350 – 963] | 610 (192) | 1.5 |
| | Fasted | 356 [223 – 559] | 370 (105) | 0.914 |
| | High fat meal | 426 [250 – 702] | 444 (143) | 1.09 |
| Ctrough,ss (ng/mL) | Reference | 130 [54.7 – 257] | 138 (62) | 1 |
| | 200 mg TID | 162 [68.1 – 320] | 172 (77.1) | 1.24 |
| | WT: 60 kg | 147 [60.8 – 295] | 157 (71.6) | 1.13 |
| | WT: 100 kg | 111 [47.5 – 216] | 117 (51.5) | 0.851 |
| | Female | 192 [91.1 – 358] | 202 (81.1) | 1.47 |
| | Severe RI | 284 [147 – 497] | 297 (108) | 2.18 |
| | Fasted | 86.3 [39.5 – 167] | 92.8 (40.4) | 0.663 |
| | High fat meal | 142 [59.7 – 281] | 151 (67.7) | 1.09 |
| AUC24h,ss (ng.hr/mL) | Reference | 5940 [3940 – 9410] | 6210 (1730) | 1 |
| | 200 mg TID | 7380 [4890 – 11700] | 7730 (2150) | 1.24 |
| | WT: 60 kg | 6880 [4570 – 10900] | 7210 (2000) | 1.16 |
| | WT: 100 kg | 4900 [3250 – 7770] | 5130 (1430) | 0.826 |
| | Female | 7670 [5090 – 12200] | 8030 (2240) | 1.29 |
| | Severe RI | 10100 [6700 – 16000] | 10600 (2950) | 1.7 |
| | Fasted | 5050 [3350 – 8020] | 5290 (1470) | 0.852 |
| | High fat meal | 6480 [4300 – 10300] | 6780 (1890) | 1.09 |

Abbreviation: AUC24h = area under the concentration-time curve during a 24 hr period; TID = three times daily; Cmax = maximum concentration; Ctrough = trough concentration; RI= renal impairment; SD = standard deviation; ss = steady-state; WT = body weight.

Note: Reference is defined male with body weight of 75 kg, normal renal function and administered 150 mg TID tablet with a standard meal. The 5th to 95th percentile presented for the exposure of 1000 simulated subjects are based on the typical PK parameters, between-subject variability, and the dose or covariate values. "Severe RI" was defined per ACH471-009 study reported "severe renal impairment" group.

[1]Relative to the median value of the reference.

Source: pk.forest.plot.r

***Special populations***

- **Impaired renal function**

**Study ACH471-009**

This Phase 1, open-label, nonrandomised, multicentre, single-dose, parallel group study in participants with normal renal function or severe renal impairment (RI) was conducted to evaluate the effect of RI on safety, tolerability, PK and PD of danicopan.

When subjects were administered a single, oral, 200-mg dose of ACH-0144471, the resulting PK parameters for plasma and urinary ACH-0144471 are summarised by renal function group and presented in Table 15 and Table 16, respectively.

**Table 15: Summary of the Plasma Pharmacokinetic Parameters for ACH-0144471**

| Parameter | Normal Renal Function (N = 8) | Severe Renal Impairment (N = 8) |
|---|---|---|
| $AUC_{0-t}$ (h*ng/mL) | 3270 (26.2) | 4830 (30.3) |
| $AUC_{0-\infty}$ (h*ng/mL) | 3300 (26.0) | 5010 (31.0) |
| $C_{max}$ (ng/mL) | 697 (26.3) | 657 (28.3) |
| $T_{max}$[a] (h) | 3.00 (1.50-4.00) | 4.00 (1.50-6.00) |
| $t_{1/2}$ (h) | 10.1 (50.1) | 11.2 (38.7) |
| CL/F (L/h) | 60.5 (26.0) | 39.9 (31.0) |
| $V_z$/F (L) | 882 (60.2) | 645 (54.5) |

Source: Table 14.2.1-2
Geometric mean (CV%) data are presented
Abbreviations: $AUC_{0-t}$ = area under the concentration-time curve from time 0 to the time of last quantifiable concentration ($T_{last}$); $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $\%AUC_{extrap}$ = percentage of $AUC_{0-\infty}$ that is due to extrapolation from the last measurable concentration to infinit CL/F = apparent total plasma clearance; $C_{max}$ = maximum observed plasma concentration; CV = coefficient of variation; N = number of subjects; $t_{1/2}$ = terminal elimination half life;
$T_{max}$ = time of the maximum observed plasma concentration; $V_z$/F = apparent volume of distribution during the terminal elimination phase.
[a] Median (min-max)
Program Location: /cvn/projects/prj/ecb/programs/000000155476/dev/tables/t_pp_itt.sas
Program Run: 11DEC2018 cvn_jwilliam7 Program Status: FINAL

**Table 16: Summary of the Urinary Pharmacokinetic Parameters of ACH-0144471**

| Parameter | Normal Renal Function (N = 8) | Severe Renal Impairment (N = 8) |
|---|---|---|
| $Ae_{0-72}$ (mg) | 0.847 (30.6) | 0.614 (27.3) |
| $Fe_{0-72}$ (%) | 0.424 (30.6) | 0.307 (27.3) |
| $CL_R$ (L/h) | 0.268 (42.9) | 0.131 (42.7) |

Source: Table 14.2.1-6
Geometric mean (CV%) data are presented.
Abbreviations: Ae = amount of drug excreted unchanged in urine; $CL_R$ = renal clearance; CV = coefficient of variation; Fe = percentage of dose excreted unchanged in urine; N = number of subjects.
Program Location: /cvn/projects/prj/ecb/programs/000000155476/dev/tables/t_up_itt.sas
Program Run: 11DEC2018 cvn_jwilliam7 Program Status: FINAL

The statistical analysis of the effect of severe RI on the PK parameters of ACH-0144471 is presented in the table below.

**Table 17: Statistical Analysis of the Renal Impairment Effect on Pharmacokinetic Parameters of ACH-0144471**

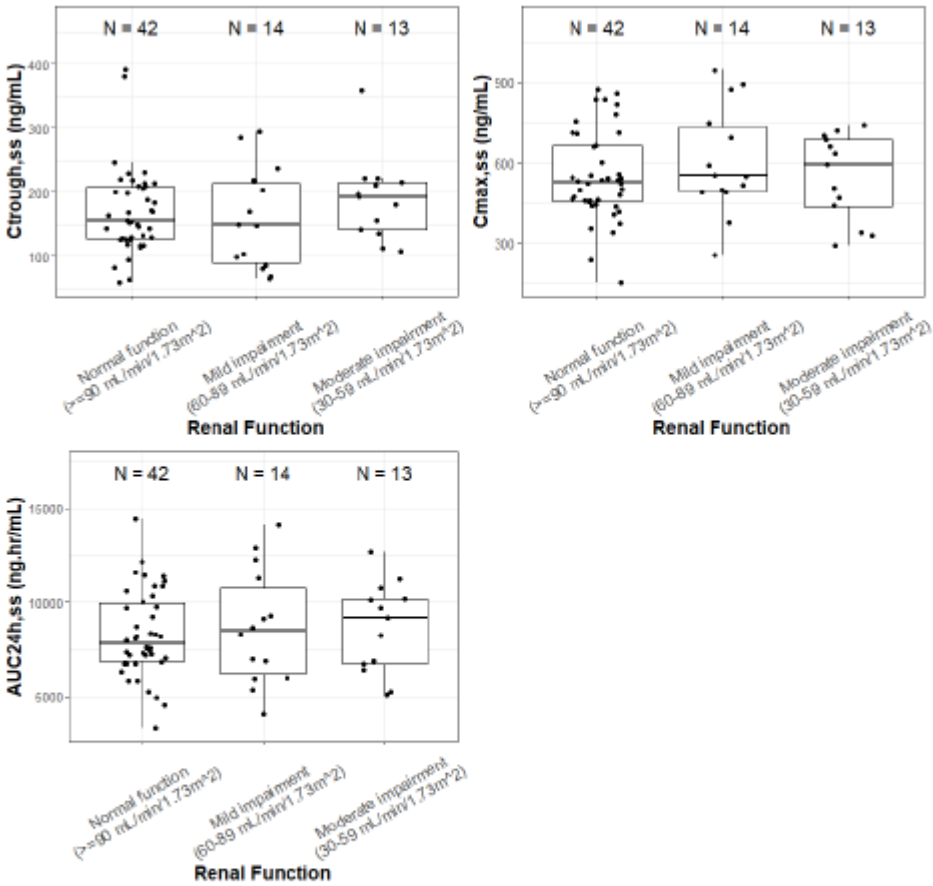
| Parameter | Renal Function Group | N | Geometric Mean | Ratio of Geometric Means (Severe : Normal) | 90% CI for the Ratio Lower | Upper | P-value |
|---|---|---|---|---|---|---|---|
| $AUC_{0-\infty}$ (h*ng/mL) | Severe RI | 8 | 5010 | | | | |
| | Normal | 8 | 3300 | 1.52 | 1.19 | 1.94 | 0.0100 |
| $AUC_{0-t}$ (h*ng/mL) | Severe RI | 8 | 4830 | | | | |
| | Normal | 8 | 3270 | 1.48 | 1.16 | 1.89 | 0.0141 |
| $C_{max}$ (ng/mL) | Severe RI | 8 | 657 | | | | |
| | Normal | 8 | 697 | 0.942 | 0.744 | 1.19 | 0.6647 |
| $t_{1/2}$ (h) | Severe RI | 8 | 11.2 | | | | |
| | Normal | 8 | 10.1 | 1.11 | 0.763 | 1.62 | 0.6320 |
| CL/F (L/h) | Severe RI | 8 | 39.9 | | | | |
| | Normal | 8 | 60.5 | 0.659 | 0.515 | 0.843 | 0.0100 |
| $CL_R$ (L/h) | Severe RI | 8 | 0.131 | | | | |
| | Normal | 8 | 0.268 | 0.486 | 0.339 | 0.698 | 0.0034 |
| $T_{max}$ (h)# | Severe RI | 8 | 4.00 | | | | |
| | Normal | 8 | 3.00 | 1.00 | 0 | 2.50 | 0.3605 |

Source: Table 14.2.1-1
Abbreviations: N = number of subjects; Normal = normal renal function; CI = confidence interval; Severe RI = severe renal impairment.
Data were analyzed using 2 sample t-test
The ratio and corresponding confidence limits are back transformed from the difference and confidence limits calculated on the loge scale
# Medians, median difference
Program Location: /cvn/projects/prj/ecb/programs/000000155476/dev/tables/t_pkanal_itt.sas
Program Run: 11DEC2018 cvn_iantys Program Status: FINAL

**Population PK analysis**

Steady state danicopan exposures were simulated for a 150 mg TID regimen using the Bayesian post-hoc PK parameters for each subject accounting for the impact of covariates and their correlation.

Subjects with mild or moderate renal impairment had similar steady state exposure as the subjects with normal renal function (Figure below).




Abbreviations: AUC24h,ss =steady state area under the curve over 24 h; Cmax,ss = steady state maximum plasma concentration; Ctrough,ss = steady state minimum (trough) plasma concentration.
Notes: Points are simulated individual PK exposure for danicopan 150 mg TID regimen at steady state. Boxplots show the median (solid bold line), the interquartile range (boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity. Renal function based on eGFR values.
Source: pk.posthoc.simulation.r

**Figure 6: Boxplots of Post Hoc Steady State Exposures from Study ALXN2040-PNH-301 by Renal Function**

- **Impaired hepatic function**

**<u>Study ACH471-012</u>**

This Phase 1, 2-part, open-label, multicentre, single-dose, parallel-group study in participants with normal hepatic function or moderate hepatic impairment was conducted to determine the effect of hepatic impairment on the safety, tolerability, and PK of danicopan.

Subjects with moderate HI (Child-Pugh Class B, scores of 7 to 9) were compared to healthy control subjects with normal hepatic function in Part 1.

The summary of plasma ACH-0144471 PK parameters is presented in Table 18.

**Table 18: Summary of Plasma ACH-0144471 Pharmacokinetic Parameters Following Administration of a Single Oral Dose of 200 mg ACH-0144471 to Subjects with Moderate Hepatic Impairment and to Healthy Matched Control Subjects (PK Analysis Population)**

| Pharmacokinetic Parameters | Moderate HI | Healthy Controls for Moderate HI |
|---|---|---|
| AUC0-t (ng*hr/mL) | 3052 (22.8) [n=8] | 3304 (13.4) [n=8] |
| AUC0-inf (ng*hr/mL) | 3061 (22.7) [n=8] | 3314 (13.2) [n=8] |
| AUC%extrap (%) | 0.3146 ± 0.41671 [n=8] | 0.2879 ± 0.26910 [n=8] |
| Cmax (ng/mL) | 482.9 (33.2) [n=8] | 665.8 (30.4) [n=8] |
| Tmax (hr) | 4.000 (2.50, 6.02) [n=8] | 2.750 (2.00, 6.00) [n=8] |
| t1/2 (hr) | 9.546 ± 4.2825 [n=8] | 9.404 ± 3.1957 [n=8] |
| Kel (1/hr) | 0.08308 ± 0.030439 [n=8] | 0.08226 ± 0.030201 [n=8] |
| CL/F (L/hr) | 66.75 ± 14.474 [n=8] | 60.82 ± 8.1536 [n=8] |
| Vz/F (L) | 940.5 ± 514.08 [n=8] | 844.3 ± 365.75 [n=8] |

Moderate HI: Administration of a single oral dose of 200 mg ACH-0144471 to subjects with moderate HI following a moderate fat meal
Healthy Controls for Moderate HI: Administration of a single oral dose of 200 mg ACH-0144471 to healthy control subjects following a moderate fat meal
AUC and Cmax values are presented as geometric mean and geometric CV%.
Tmax values are presented as Median (Minimum, Maximum).
Other parameters are presented as arithmetic mean ± SD.
Source: Tables 14.2.1.3 and 14.2.1.4
Program: /CA23863/sas_prg/pksas/adam_intext_pkparam.sas 02APR2019 4:50

The statistical comparisons of plasma ACH-0144471 PK parameters are summarised in Table 19.

**Table 19: Summary of Statistical Comparisons of Plasma ACH-0144471 Pharmacokinetic Parameters Following Administration of a Single Oral Dose of 200 mg ACH-0144471 to Subjects with Moderate Hepatic Impairment Versus Healthy Matched Control Subjects (PK Analysis Population)**

| Parameter | Moderate HI (Test) | | Healthy Controls for Moderate HI (Reference) | | GMR (%) | 90% Confidence Interval | P-Value |
|---|---|---|---|---|---|---|---|
| | Geometric Means | n | Geometric Means | n | | | |
| AUC0-t (ng*hr/mL) | 3052 | 8 | 3304 | 8 | 92.35 | 78.47 - 108.69 | 0.4042 |
| AUC0-inf (ng*hr/mL) | 3061 | 8 | 3314 | 8 | 92.38 | 78.58 - 108.60 | 0.4025 |
| Cmax (ng/mL) | 482.9 | 8 | 665.8 | 8 | 72.53 | 55.17 - 95.35 | 0.0577 |

Healthy Controls for Moderate HI: Administration of a single oral dose of 200 mg ACH-0144471 to healthy control subjects following a moderate fat meal
Moderate HI: Administration of a single oral dose of 200 mg ACH-0144471 to subjects with moderate HI following a moderate fat meal
Geometric means are calculated by exponentiating the means derived from the 2-sample t-test analysis.
Geometric Mean Ratio = Moderate/Healthy derived from the 2-sample t-test analysis. P-values and confidence intervals were calculated assuming equal variances (p-value for F-test greater than 0.05).
Source: Table 14.2.1.6
Program: /CA23863/sas_prg/pksas/adam_intext_statsmixed.sas 02APR2019 4:52

Geometric mean ratios of plasma ACH-0144471 AUC0-t, AUC0-inf, and $C_{max}$ were approximately 8%, 8%, and 27% lower, respectively, following administration of 200 mg ACH-0144471 to subjects with moderate HI compared to healthy matched control subjects.

- **Gender**

**Population PK analysis**

The impact of sex on PK was reevaluated in the current covariate analysis, along with other covariates of interest.

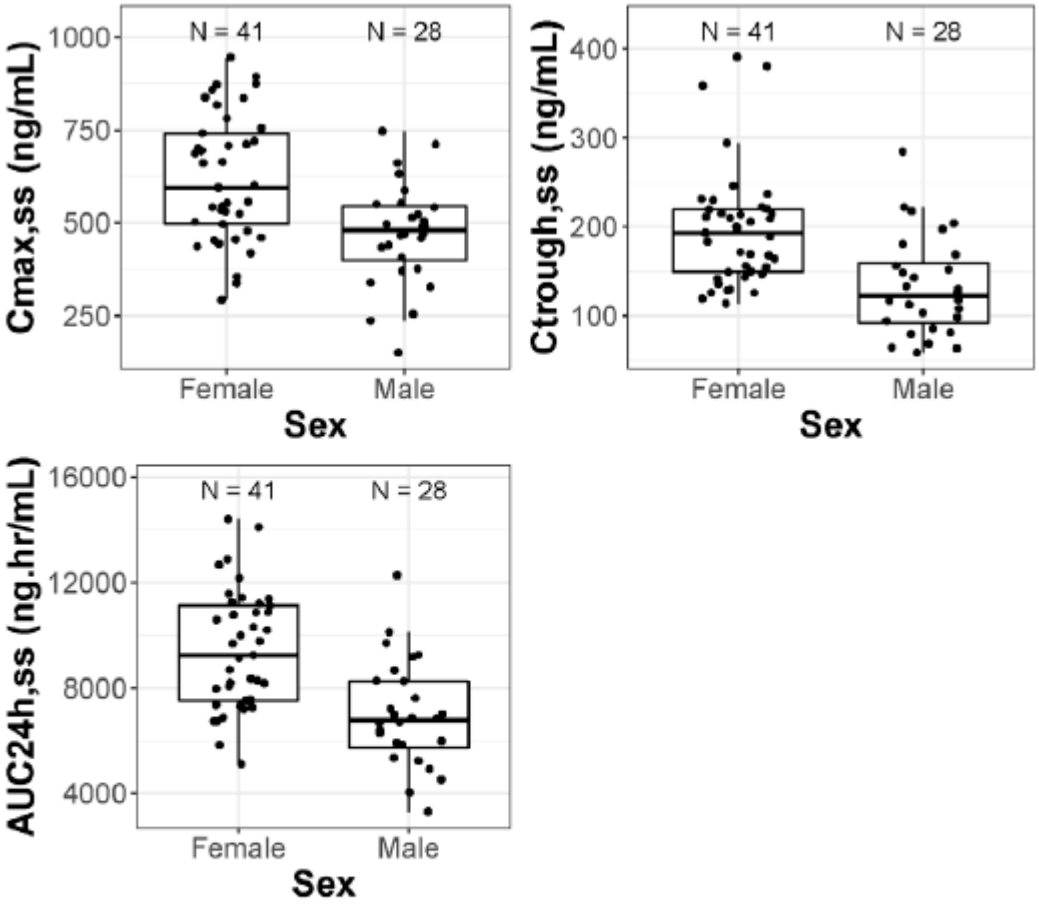
Sex on CL/F was retained in the final model. CL/F was reduced by 22.7% in females.

The impact of covariates included in the final PPK model was evaluated using forest plots of relative changes in steady state exposure assuming a 150 mg TID regimen (unless otherwise noted) when covariates were varied one at a time (i.e., univariate analysis) (Figure 5). A statistical summary of the simulated exposures is provided in Table 14 (See Target Population section).

Female subjects had a 29% higher AUC compared to males.

Steady state danicopan exposures were simulated for a 150 mg TID regimen using the Bayesian post-hoc PK parameters for each subject accounting for the impact of covariates and their correlation.

Mean steady state exposures were higher in females compared to males (Figure 7).




Abbreviations: AUC24h,ss =steady state area under the curve over 24 h; Cmax,ss = steady state maximum plasma concentration; Ctrough,ss = steady state minimum (trough) plasma concentration.
Notes: Points are simulated individual PK exposure for danicopan 150 mg TID regimen at steady state. Boxplots show the median (solid bold line), the interquartile range (boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity
Source: pk.posthoc.simulation.r

**Figure 7: Boxplots of Post Hoc Steady State Exposures from Study ALXN2040-PNH-301 by Sex**

- **Race**

**<u>Study ALXN2040-HV-101</u>**

This open-label, randomised, single-dose, 3-period, 3-treatment crossover study of danicopan (200 mg fasting, 200 mg fed, 400 mg fed) Phase 1 study in healthy adult Japanese participants was conducted to determine the safety, tolerability, and PK of danicopan after administration as an oral tablet in healthy participants of Japanese descent.

A comparison of PK data in Japanese participants (Study ALXN2040-HV-101) versus non-Japanese participants (Study ACH471-016) is summarised in Table 20.

**Table 20: Comparison of PK Parameters of Danicopan between Japanese (Study ALXN2040-HV-101) and Non-Japanese (Study ACH471-016) Participants: Arithmetic Mean Values (PK analysis set)**

| PK Parameter (unit) | Japanese (N = 9) | Non-Japanese (N = 17) | Ratio (Japanese:Non-Japanese) |
|---|---|---|---|
| **Treatment A (200 mg Fasting)** | | | |
| $AUC_{0-t}$ (h × ng/mL) | 3018 | 2802 | 1.0771 |
| $AUC_{0-inf}$ (h × ng/mL) | 3059 | 2812 | 1.0878 |
| $C_{max}$ (ng/mL) | 651.4 | 479.8 | 1.3576 |
| $T_{max}$ (h) | 3.000 | 2.591 | 0.4090[a] |
| $t_{½}$ (h) | 8.989 | 8.757 | 1.0265 |
| **Treatment B (200 mg Fed)** | | | |
| $AUC_{0-t}$ (h × ng/mL) | 4196 | 3615 | 1.1607 |
| $AUC_{0-inf}$ (h × ng/mL) | 4201 | 3620 | 1.1605 |
| $C_{max}$ (ng/mL) | 883.2 | 878.3 | 1.0056 |
| $T_{max}$ (h) | 3.707 | 3.088 | 0.6190[a] |
| $t_{½}$ (h) | 6.853 | 7.249 | 0.9454 |

Note: Treatment A = danicopan 200 mg oral under fasting conditions; Treatment B = danicopan 200 mg oral under fed conditions.

[a] For $T_{max}$, the difference is presented.

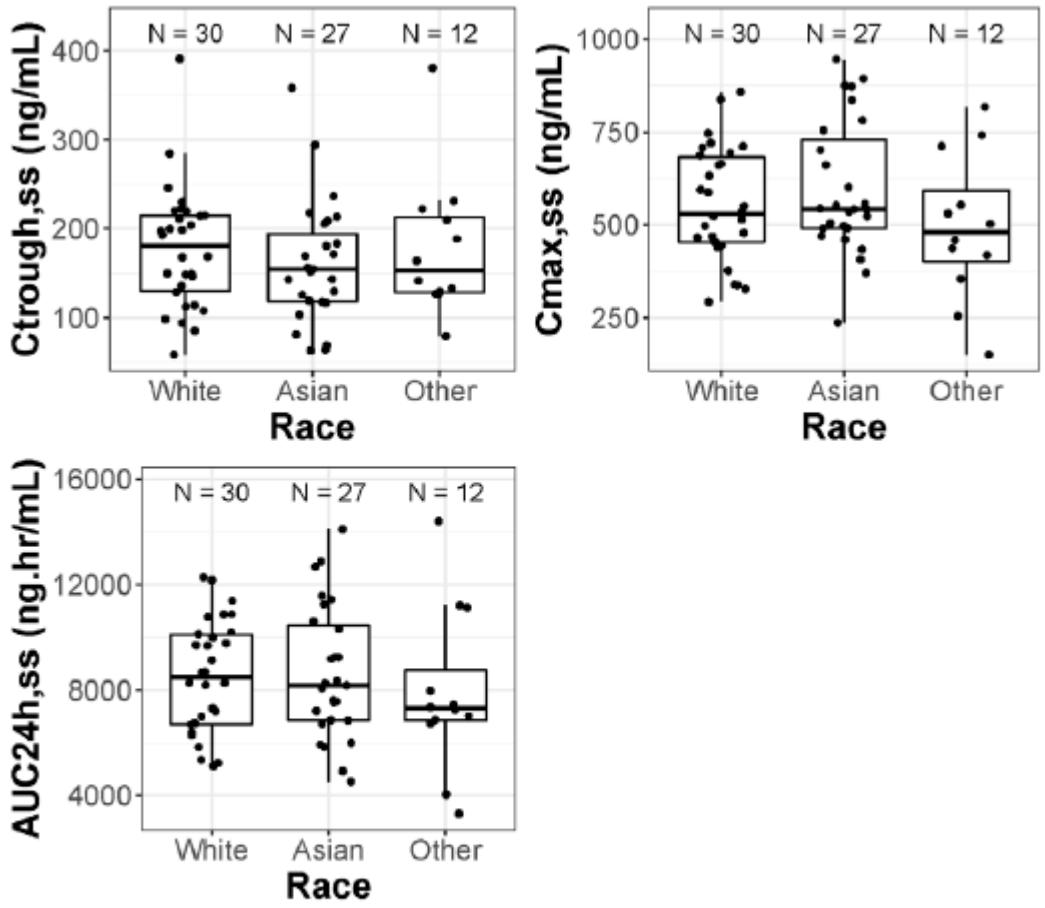
Abbreviations: $AUC_{0-inf}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-t}$ = area under the concentration-time curve from time 0 to time t; $C_{max}$ = maximum observed concentration; h = hour(s); PK = pharmacokinetic; $t_{½}$ = terminal elimination half-life; $T_{max}$ = time taken to reach maximum observed concentration

Source: ALXN2040-HV-101 CSR Table 14.2.1.3

**Population PK analysis**

Steady state danicopan exposures were simulated for a 150 mg TID regimen using the Bayesian post-hoc PK parameters for each subject accounting for the impact of covariates and their correlation.

The range of exposures was similar among different race (Figure 8).




Abbreviations: AUC24h,ss =steady state area under the curve over 24 h; Cmax,ss = steady state maximum plasma concentration; Ctrough,ss = steady state minimum (trough) plasma concentration.
Notes: Points are simulated individual PK exposure for danicopan 150 mg TID regimen at steady state. Boxplots show the median (solid bold line), the interquartile range (boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity

**Figure 8: Boxplots of Post Hoc Steady State Exposures from Study ALXN2040-PNH-301 by race**

- **Weight**

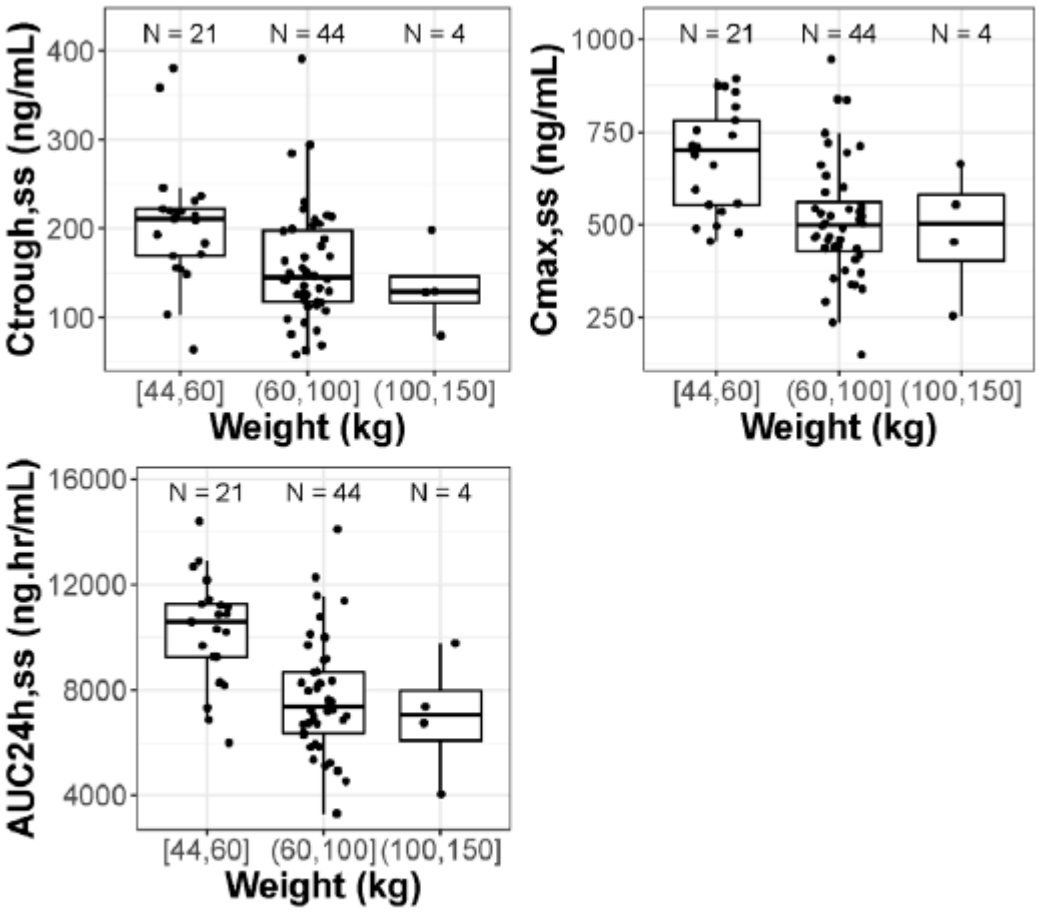
The effect of body weight on danicopan PK, was modelled on the volume terms (Vc/F and Vp/F) and on the clearance terms (CL/F and Q/F).

The impact of covariates included in the final PPK model was evaluated using forest plots of relative changes in steady state exposure assuming a 150 mg TID regimen (unless otherwise noted) when covariates were varied one at a time.

$C_{max}$,ss, Ctrough,ss and AUC24h,ss decreased in subjects with increasing body weight, and for the body weight range of 60 to 100 kg relative to median body weight of 75kg, the ratios of exposure parameters were within the 0.8-1.25 range and therefore the differences are considered clinically insignificant.

Steady state danicopan exposures were simulated for a 150 mg TID regimen using the Bayesian post-hoc PK parameters for each subject accounting for the impact of covariates and their correlation.

Mean steady state exposures were higher in subjects in the lower body weight quartile compared to the highest body weight quartile (Figure 9).




Abbreviations: AUC24h,ss =steady state area under the curve over 24 h; Cmax,ss = steady state maximum plasma concentration; Ctrough,ss = steady state minimum (trough) plasma concentration.
Notes: Points are simulated individual PK exposure for danicopan 150 mg TID regimen at steady state. Boxplots show the median (solid bold line), the interquartile range (boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity.

**Figure 9: boxplots of Post Hoc Steady State Exposures from Study ALXN2040-PNH-301 by Body Weight**

- **Elderly**

**Study ACH471-016** Part 2 was a 1-period, single-dose pharmacokinetic (PK) study in healthy elderly participants. On Day 1, participants received a single 200 mg dose of danicopan (2x 100 mg tablets) with a moderate-fat meal. PK blood samples were collected for danicopan predose and for 72 hours following danicopan administration.

A total of 7 participants were enrolled in Part 2 of the study. All 7 participants completed the study treatment as per protocol and were included in the PK and safety analyses.

Part 2 was conducted to collect PK data in a cohort of healthy elderly participants for comparison with PK data from young healthy adults. Though statistical analysis comparing PK data from elderly participants (Part 2) to PK data from healthy young adult participants in Part 1 under fed conditions was performed, variables could confound the assessment of age on danicopan PK (i.e., different caloric content of the meals in Part 2 vs Part 1). Therefore, only the descriptive analysis of the danicopan PK profile and PK parameter estimates for healthy elderly participants is presented.

**Population PK analysis**

Age was evaluated as a covariate in the PK parameters (CL/F, Vc/F) and did not meet the statistical significance threshold.

The distribution of patients across the different sub-groups of age for the PK trials is shown in the table below.

**Table 21: Distribution of Patients Across The Different Sub-Groups Of Age For The PK Trials**

| | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| PK Trials[a] | 17/419 | 2/419 | 0/419 |

[a] Includes 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, and ALXN2040-HV-119.

***Pharmacokinetic interaction studies***

Available nonclinical data showed non-CYP based metabolism is the predominant clearance pathway for danicopan. The minimal contribution of CYP metabolism in human hepatocytes is suggestive of a very low likelihood of danicopan as a victim of CYP based drug-drug interactions. As a P-gp transporter substrate with high permeability and low efflux ratio, the oral exposure of danicopan does not appear to be affected by P-gp efflux in the gastrointestinal tract. Danicopan is not a substrate of BCRP, OATP1B1, and OATP1B3 transporters. Thus, danicopan is considered to have no or low likelihood to be a victim of drug-drug interactions due to inhibition of these drug transporters.

**Study ACH471-010**

This Phase 1 DDI, single-centre, 3-part, open-label, fixed-sequence, 2-treatment study was conducted to determine the potential drug interaction, safety, and tolerability between danicopan and midazolam, fexofenadine, and mycophenolate mofetil (MMF) in healthy adult participants.

Part 1

- Following administration of a single oral dose of midazolam administered in the presence of ACH-0144471, midazolam AUC0-t, AUC0-inf, and $C_{max}$ were increased by 22% - 23% relative to midazolam administered alone.
- A single dose of midazolam did not appear to have any effect on ACH-0144471 AUC or $C_{max}$ following multiple doses.

Part 2

- Following administration of a single oral dose of fexofenadine in the presence of ACH-0144471, fexofenadine $C_{max}$ was increased by 42%, fexofenadine AUC0-t was increased by 60%, and fexofenadine AUC0-inf was increased by 62% relative to fexofenadine administered alone. The time to reach peak exposure was significantly delayed by 45 minutes ($p < 0.05$).
- A single dose of fexofenadine did not appear to have any effect on ACH-0144471 AUC or $C_{max}$ following multiple doses.

Part 3

- Following administration of a single oral dose of MMF in the presence of ACH-0144471, the PK of the MMF metabolite MPA was unchanged relative to MMF administered alone. The AUC0-t and AUC0-inf of the metabolite MPAG were unchanged relative to MMF administered alone while MPAG $C_{max}$ was slightly decreased, an effect that is likely not clinically significant.
- A single dose of MMF had no effect on ACH-0144471 AUC but slightly decreased $C_{max}$.

**Study ACH471-014**

This Phase 1 DDI 3-part (conducted concurrently), open-label, fixed-sequence, 2-period study was conducted to evaluate the potential drug interaction, and safety and tolerability between danicopan and cyclosporine, tacrolimus, antacids, and omeprazole in healthy adult participants.

Part 1

- Following administration of a single oral dose of cyclosporine administered in the presence of ACH-0144471, whole blood cyclosporine AUC0-t and AUC0-inf increased by approximately 18%-20% and the time to reach peak exposure was significantly delayed by 13 minutes ($p < 0.05$) relative to cyclosporine administered alone. Whole blood cyclosporine $C_{max}$ was not impacted by the presence of ACH-0144471.
- A single dose of cyclosporine increased plasma ACH-0144471 exposure following multiple doses by 14% and 21% for $C_{max}$ and AUC0-8, respectively. Plasma ACH-0144471 $T_{max}$ was not impacted by the presence of cyclosporine.

Part 2

- Following administration of a single oral dose of tacrolimus in the presence of ACH-0144471, whole blood tacrolimus AUC0-t and AUC0-inf increased by approximately 49%-55% relative to tacrolimus administered alone. Whole blood tacrolimus $C_{max}$ increased by approximately 14% and $T_{max}$ was not impacted by the presence of ACH-0144471.
- A single dose of tacrolimus increased the plasma ACH-0144471 exposure following multiple doses by approximately 19% and 20% for $C_{max}$ and AUC0-8, respectively. Plasma ACH-0144471 $T_{max}$ was not impacted by the presence of tacrolimus.

Part 3

- Following administration of a single oral dose of antacids (either calcium carbonate or aluminum/magnesium hydroxide/simethicone) in the presence of ACH-0144471, plasma ACH-0144471 AUC0-8 and $C_{max}$ increased by approximately 22% and 31%, respectively, relative to ACH-0144471 administered alone. ACH-0144471 $T_{max}$ was not impacted by the presence of calcium carbonate but was significantly shortened by 33 minutes ($p < 0.05$) in the presence of aluminum/magnesium hydroxide/simethicone.
- Following administration of multiple oral doses of omeprazole in the presence of ACH-0144471, plasma ACH-0144471 $C_{max}$ increased by approximately 22% relative to ACH-0144471 administered alone and $T_{max}$ was significantly shortened by 46 minutes ($p < 0.05$). Plasma ACH-0144471 AUC0-8 was not significantly impacted.
- ACH-0144471 increased plasma omeprazole exposure by approximately 17% and 24% for AUC0-24 and $C_{max}$, respectively. Omeprazole $T_{max}$ was not impacted by the presence of ACH-0144471.

- ACH-0144471 increased plasma 5-OH omeprazole exposure by approximately 6% and 11% for AUC0-24 and $C_{max}$, respectively. 5-OH Omeprazole $T_{max}$ was not impacted by the presence of ACH-0144471.

**Study ACH471-017**

This study was conducted in 3 parts to assess the 2-way interaction between warfarin (Part 1), bupropion (Part 2), and ethinyl estradiol and norethindrone (EE and NET) (Part 3) with ACH-0144471. In each part, multiple oral doses of ACH-0144471 were administered to maximise concentrations at the time of a possible interaction.

Pharmacokinetics

Part 1:

- The extent (AUC0-t and AUC0-inf) and peak ($C_{max}$) exposures to R- and S-warfarin following coadministration of warfarin with ACH-0144471 were similar to that after administration of warfarin alone when evaluated using 90% CI of geometric means test (< 6% and 14% difference in R- and S-warfarin exposure, respectively). The times to reach peak R- and S-warfarin exposure ($T_{max}$) were not significantly different between the administration of warfarin alone and coadministered with ACH-0144471.
- A single dose of warfarin decreased plasma ACH-0144471 exposure as measured by AUC0-8 and $C_{max}$ by 17% and 19%, respectively, when administered while subjects were receiving multiple doses of ACH-0144471. $T_{max}$ for ACH-0144471 was not significantly different between the administration of ACH-0144471 alone and coadministered with warfarin.

Part 2:

- The extent (AUC0-t and AUC0-inf) and peak ($C_{max}$) exposures to bupropion following coadministration with ACH-0144471 were similar to that after administration of bupropion alone when evaluated using 90% CI of geometric means test (with relatively small increases of ~12% and ~5%, respectively). The extent and peak exposures to hydroxybupropion following coadministration with ACH-0144471 were similar to that after administration of bupropion alone with small decreases of ~3% and ~7%, respectively.
- A single dose of bupropion decreased plasma ACH-0144471 exposure (AUC0-8 and $C_{max}$) by approximately 12% to 14%, respectively, when administered while subjects were receiving multiple doses of ACH-0144471. $T_{max}$ for ACH-0144471 was not statistically different between the administration of ACH-0144471 alone and coadministered with bupropion.

Part 3:

- Administration of ACH-0144471 TID with EE/NET increased the exposure of both EE (by 7% to 30% for $C_{max}$ and AUCs, respectively) and NET (by 13% to 14%, for $C_{max}$ and AUCs, respectively) compared to dosing of EE/NET alone when evaluated using 90% CI of geometric means test. $T_{max}$ for EE was not significantly different between the administration of EE/NET alone and coadministered with ACH-0144471. However, $T_{max}$ for NET was statistically different between the administration of EE/NET alone ($T_{max}$ = 2.25 hours) and coadministered with ACH-0144471 ($T_{max}$ = 3.08 hours), which may not be clinically significant.
- A single dose of EE/NET decreased plasma ACH-0144471 exposure (AUC0-8 and $C_{max}$) by approximately 17% and 14%, respectively, when administered while subjects were receiving multiple doses of ACH-0144471.

Pharmacodynamics

Part 1:

Administration of warfarin after ACH-0144471 TID dosing had no effect on the pharmacodynamics (INR AUC0-168 and $INR_{max}$) of warfarin compared to dosing warfarin alone.

### *2.6.2.2. Pharmacodynamics*

The primary PD endpoints assessed in the danicopan clinical development programme were ex vivo AP activity and serum Bb concentrations, while total FD and C3 concentrations and CP activity were assessed as exploratory biomarkers. Additionally, in pivotal Study ALXN2040-PNH-301, where patients received stable treatments with C5 inhibitors (ravulizumab or eculizumab), serum free C5 concentrations were also evaluated.

The extent of AP inhibition of danicopan was measured by semi-quantitative, ex vivo AP activity assays. The AP Wieslab (APW) assay was utilised in early development studies, switching to the AP Hemolytic (APH) assay in pivotal Study ALXN2040-PNH-301, which included concomitant administration of C5 inhibitors (ravulizumab or eculizumab), because the APH assay is more sensitive to complement activity in the presence of C5 inhibitors than the APW assay. In both AP assays, the values are calculated relative to normal human serum and are expressed in units of percent. A change from Baseline in AP activity of $\geq$ 90% or remaining AP activity < 10% is considered to represent complete AP activity inhibition.

***Mechanism of action***

Danicopan binds reversibly to FD and acts as a selective inhibitor of FD function and consequently of AP activation.

Danicopan can inhibit the AP-mediated deposition of C3 fragments on PNH red blood cells; such deposition is a key cause of the EVH that is observed in a small subset of patients with PNH on treatment with a C5 inhibitor.

Pharmacodynamic data from studies in healthy volunteers and patients with PNH demonstrate that danicopan significantly inhibits the AP of complement system, as demonstrated by ex vivo biomarker of serum AP activity and *in vivo* biomarker of plasma Bb concentration. Additionally, studies in patients with PNH have established that danicopan reduces the complement C3 fragment deposition on circulating PNH red blood cells.

In single-ascending and multiple-ascending dose studies in healthy volunteers, danicopan conferred dose-dependent inhibition of AP activity across a variety of dosing regimens. In addition, Bb concentration was substantially reduced in all dosing cohorts. As Bb is a cleavage product formed directly by the action of FD, this reduction provides a direct demonstration that danicopan inhibits FD *in vivo*.

***Primary and Secondary pharmacology***

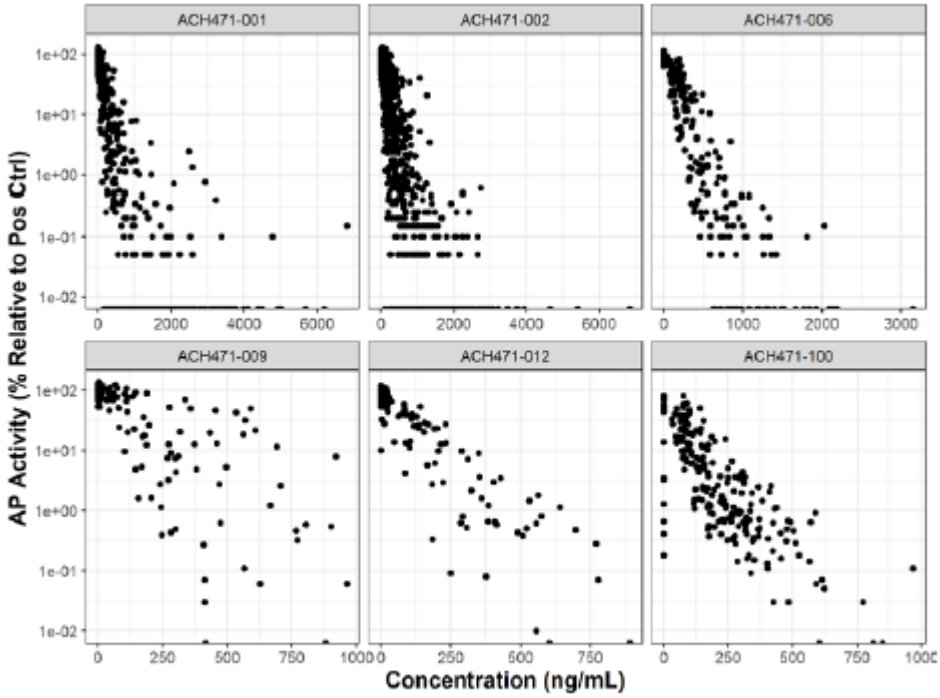
**PK-PD of APW**

Explore and quantify the relationship between danicopan plasma concentrations and alternative pathway activity by Wieslab assay (APW)

This analysis included a subset of studies in which the APW results were available. The PK-PD data set included 2567 APW measurements from 120 subjects, including 2375 APW measurements from 110

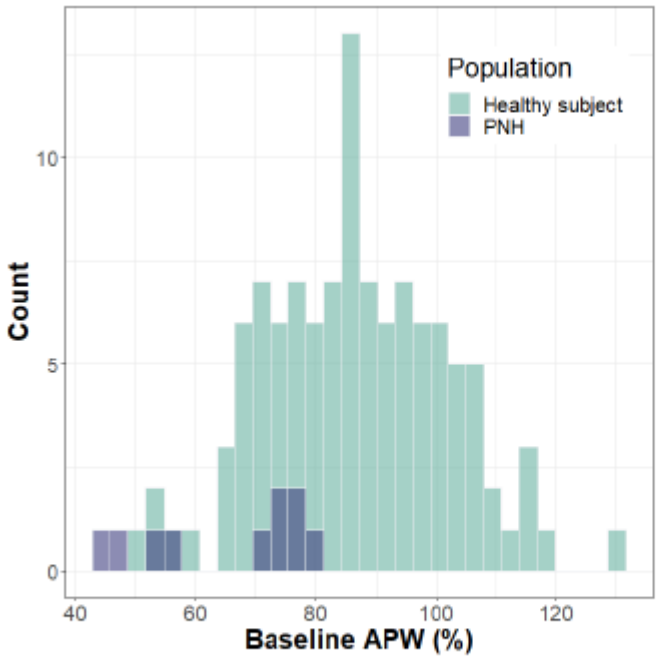
healthy subjects and 192 APW measurements from 10 patients with PNH. A total of 392 (15%) were BLQ.

Figure 10 shows individual APW concentration versus danicopan observed concentration (semilog), stratified by study. Figure 11 shows the distribution of baseline APW in the overall study population and by study.




Source: 2022-03-29 APW exploratory.12_hlv3.r

**Figure 10: APW versus Danicopan Observed Concentration by Study**




Abbreviations: PNH = Paroxysmal nocturnal hemoglobinuria; APW = alternative pathway activity by Wieslab assay.
Source: pk.apw.sim.r

**Figure 11: Histogram of Baseline APW**

Base APW Model

Model development was guided by evaluation of exploratory plots. A log-linear model described the relationship between danicopan observed concentrations and APW. This model had a lower Bayesian Information Criterion (BIC) than an $E_{max}$ model (11770 vs. 11876). The model was parameterised in terms of baseline APW (BASE) and a first order rate constant (KK, relative to danicopan concentration, not time).

The model was estimated with imputation of the first BLQ by LLOQ/2 and removal of subsequent BLQ (M6 method). Re-estimation of the model using all data (including BLQ values set to 0), excluding BLQ values (M1 method), and with treatment of BLQ values as censored (M3 method) yielded similar estimates of KK (<10% difference).

Covariate effects

Candidate covariates were selected by screening covariates and ETAs and introducing them into the base APW model one at a time in a stepwise forward addition process. These were PNH on BASE, and baseline APW, baseline Factor D and PNH on KK. Significant covariates were retained in a full model; covariates that were not significant on backward deletion of covariates one at a time from the full model were excluded. After exclusion of these covariates, the resultant model, including PNH on BASE and baseline APW on KK, was considered the final APW model.

Final APW Model

The final APW model parameter estimates are presented in Table 22.

**Table 22: Population Parameter Estimates for the Final APW Model**

| Parameter | Unit | Estimate | RSE (%) | Shrinkage (%) |
|---|---|---|---|---|
| BASE | | 81.3 | 2.74 | |
| KK | 1/ng/mL | 0.00709 | 4.93 | |
| BAPW on KK | | -1.34 | 17.1 | |
| PNH on BASE | | 0.681 | 12.8 | |
| IIV | | | | |
| $\omega^2$_BASE* | | 202 | 20.0 | 2.30 |
| $\omega^2$_KK | | 0.259 | 14.2 | 2.58 |
| Residual Error | | | | |
| Proportional | | 0.319 | 18.9 | |
| Additive | | 0.498 | 3.95 | |

Abbreviations: BAPW = observed baseline APW; BASE = estimated baseline APW; IIV = interindividual variability; KK = first order rate constant, relative to danicopan concentration; PNH = paroxysmal nocturnal hemoglobinuria.

Notes: * - additive IIV on BASE. RSE calculated as standard error/estimate x 100. Shrinkage on the residual error was 2.68%. The typical concentration that produces 50% decrease from baseline ($IC_{50}$) was calculated to be 92 ng/mL and typical concentration that produces 90% decrease from baseline ($IC_{90}$) was calculated to be 306 ng/mL in healthy subjects. Baseline APW was calculated to be 55% in PNH patients. Typical $IC_{50}$ and $IC_{90}$ were calculated to be 55 ng/mL and 183 ng/mL, respectively, in PNH patients.

Source: PD_run187.lst

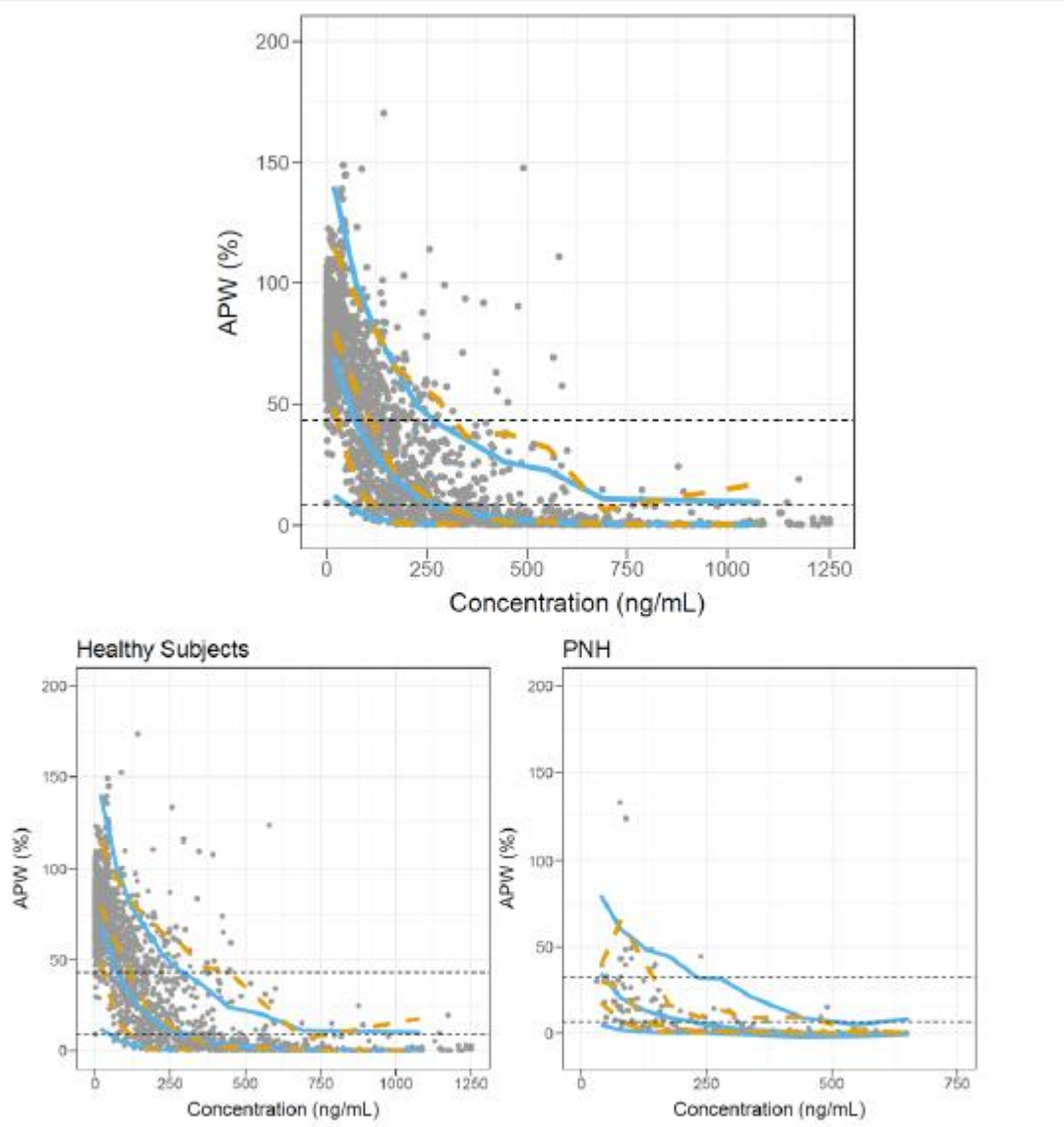
The final model parameter and covariate relationship are given as:

$$BASE_i = 81.3 \times [0.681(if\ PNH)]$$

$$KK_i = 0.00709 \times (\frac{BAPW_i}{85})^{-1.34}$$

where subscript i represents patient i, BAPW = observed baseline APW, BASE = estimated baseline APW, KK = first order rate constant, relative to danicopan concentration, PNH =paroxysmal nocturnal haemoglobinuria.

Figure 12 presents pcVPCs by study population.

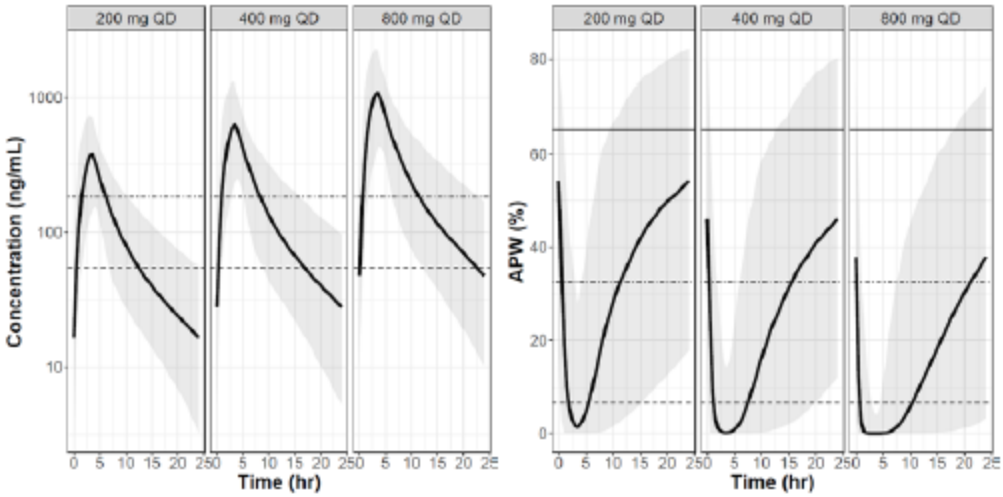



Abbreviations: APW = Alternative pathway activity by Wieslab assay; pcVPC = prediction-corrected visual predictive check; PNH = paroxysmal nocturnal hemoglobinuria.
Notes: Grey dots are individual prediction-corrected values. Yellow dashed lines represent the 5th, 50th (median) and 95th percentiles of the observed APW over concentration. Solid blue lines represent the 5th, 50th (median) and 95th percentiles of the predictions from 1000 simulations. Dashed lines indicate 50% and 90% of inhibition in patients with APW.
Source: gof-v6.r

**Figure 12: pcVPC for Final APW Model, Overall and by Study Population**

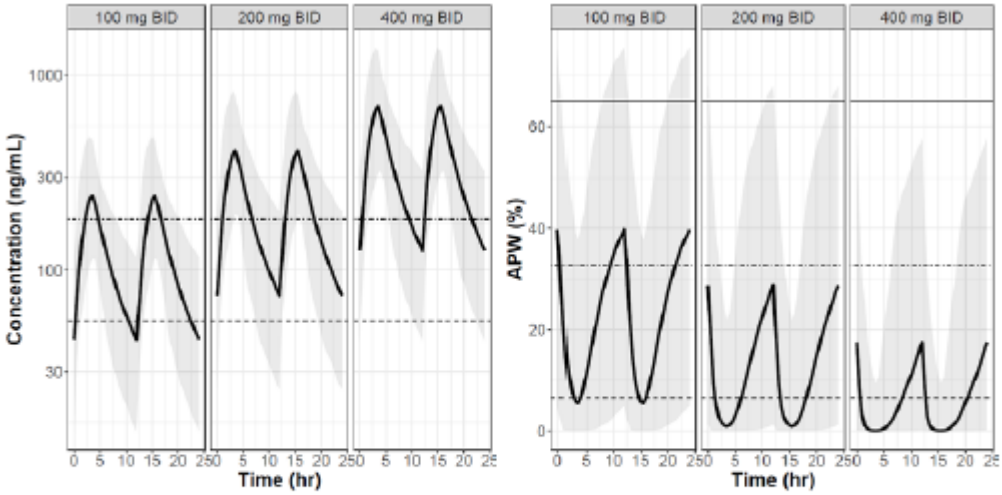
PK-PD Simulations

Simulated PK and APW profiles are illustrated in Figure 13, Figure 14, Figure 15, and Figure 16, for the QD regimens, BID regimens, TID regimens, and QID regimens, respectively. The simulations were done for the PNH population with danicopan tablet administered with standard meal.



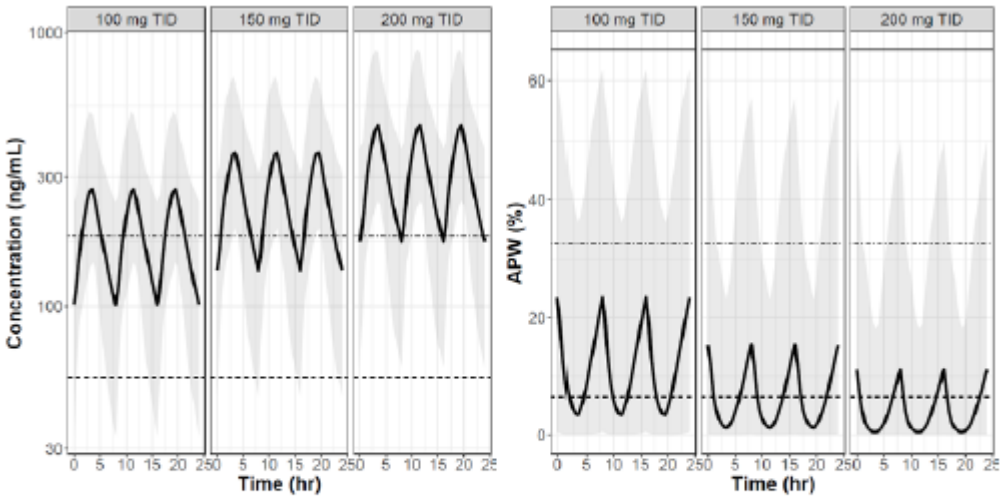

Abbreviations: PK = pharmacokinetics; APW = alternative pathway activity by Wieslab assay; QD = once daily.
Notes: Black lines are median and gray area are [2.5 to 97.5%ile] of 1000 simulated subjects at steady state. Dashed horizonal lines in the PK panels indicate the PK concentrations at IC50 (upper line) and IC90 (lower line) of APW inhibition in patients with PNH. Solid horizonal line in the APW panels indicates mean baseline APW observed in subjects with PNH, and dashed lines indicate 50% and 90% of inhibition.
Source: pk.apw.sim.r

**Figure 13: Simulated Steady State PK and APW for QD Regimens**




Abbreviations: PK = pharmacokinetics; APW = alternative pathway activity by Wieslab assay; BID = twice daily.
Notes: Black lines are median and gray area are [2.5 to 97.5%ile] of 1000 simulated subjects at steady state. Dashed horizonal lines in the PK panels indicate the PK concentrations at IC50 (upper line) and IC90 (lower line) of APW inhibition in patients with PNH. Solid horizonal line in the APW panels indicates mean baseline APW observed in subjects with PNH, and dashed lines indicate 50% and 90% of inhibition.
Source: pk.apw.sim.r

**Figure 14: Simulated Steady State PK and APW for BID Regimens**

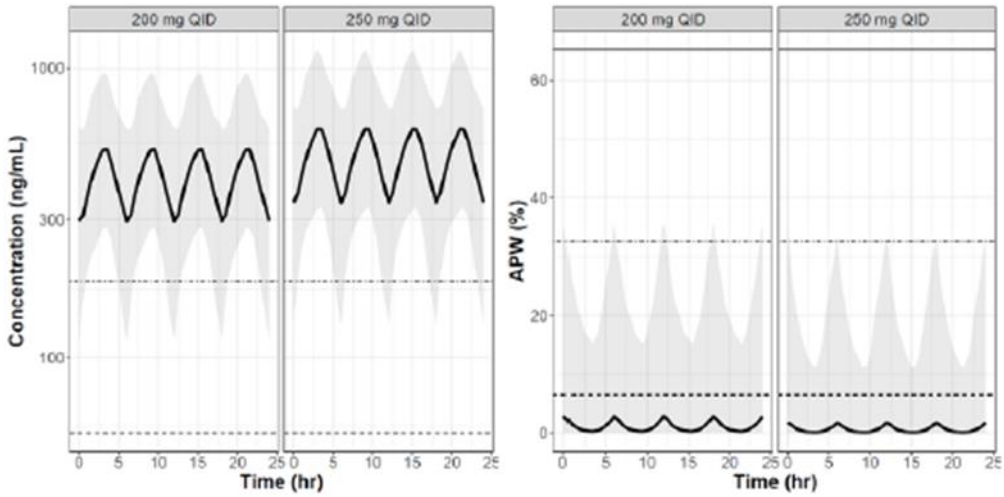



Abbreviations: : PK = pharmacokinetics; APW = alternative pathway activity by Wieslab assay; TID = three times per day.

Notes: Black lines are median and gray area are [2.5 to 97.5%ile] of 1000 simulated subjects at steady state. Dashed horizonal lines in the PK panels indicate the PK concentrations at IC50 (upper line) and IC90 (lower line) of APW inhibition in patients with PNH. Solid horizonal line in the APW panels indicates mean baseline APW observed in subjects with PNH, and dashed lines indicate 50% and 90% of inhibition.

Source: pk.apw.sim.r

**Figure 15: Simulated Steady State PK and APW for TID Regimens**




Abbreviations: : PK = pharmacokinetics; APW = alternative pathway activity by Wieslab assay; QID = four times per day.

Notes: Black lines are median and gray area are [2.5 to 97.5%ile] of 1000 simulated subjects at steady state. Dashed horizonal lines in the PK panels indicate the PK concentrations at IC50 (upper line) and IC90 (lower line) of APW inhibition in patients with PNH. Solid horizonal line in the APW panels indicates mean baseline APW observed in subjects with PNH, and dashed lines indicate 50% and 90% of inhibition.

Source: pk.apw.sim.r

**Figure 16: Simulated Steady State PK and APW for QID Regimens**

**Table 23: Simulated Steady State PK and APW Parameters for Different Regimens**

| | PK | | | APW | | |
|---|---|---|---|---|---|---|
| Regimen | Cmax,ss (ng/mL) | Ctrough,ss (ng/mL) | Daily AUC,ss (ng.hr/mL) | % Inhibition at trough | % Average inhibition | Mean % duration of >90% inhibition |
| 200 mg QD | 383.6 [160.7, 790.5] | 16.2 [3.1, 60] | 2444.1 [1431.4, 4585] | 15.9 [2.6, 62.2] | 50.1 [22.8, 86.6] | 16.9 |
| 400 mg QD | 646.8 [268.1, 1303.4] | 28.2 [5.7, 97.7] | 4153.8 [2422.7, 7837.1] | 25.5 [3.8, 81.1] | 63.2 [31.5, 95.2] | 28.8 |
| 800 mg QD | 1079.3 [444.3, 2182.8] | 46.8 [9, 164.8] | 7018.3 [4032.6, 13555.2] | 38.8 [7.3, 95.3] | 75.7 [42.4, 99.1] | 43.4 |
| 100 mg BID | 247.5 [115.2, 488.3] | 43.5 [14.6, 118.8] | 2853.4 [1655.8, 5420.6] | 36.6 [9.1, 90.5] | 64.5 [28.7, 97.2] | 20.8 |
| 200 mg BID | 421.4 [199.1, 854.6] | 72.7 [24.5, 214.9] | 4843.1 [2866.4, 9274.7] | 54.2 [14.3, 98.5] | 79.5 [38.7, 99.6] | 41.1 |
| 400 mg BID | 719.6 [336.5, 1438.4] | 125.3 [43.3, 347.2] | 8334.6 [4740.4, 15889.1] | 72.2 [25.7, 99.9] | 90.5 [57.5, 100] | 63.1 |
| 100 mg TID | 274.5 [147, 550.4] | 97.1 [34.2, 234.9] | 4298.3 [2558.3, 8259.1] | 63.6 [20.1, 98.5] | 81.2 [37.6, 99.5] | 38.1 |
| 150 mg TID | 376.2 [201.8, 773.6] | 132.4 [47.8, 319.3] | 5833.8 [3485.9, 11488.5] | 76.4 [27.9, 99.7] | 89.8 [51.7, 99.9] | 55.1 |
| 200 mg TID | 468.3 [241.1, 933.3] | 165.8 [58.3, 402.6] | 7323.8 [4237.5, 14368.1] | 81.9 [32.9, 100] | 93.2 [57.2, 100] | 64.2 |
| 200 mg QID | 525.6 [290.2, 1039.2] | 282.9 [115.1, 606.3] | 9891.9 [5732.3, 18773] | 95.2 [55.9, 100] | 97.9 [68.9, 100] | 80.5 |
| 250 mg QID | 636.9 [341.7, 1286.7] | 344.3 [135.8, 725] | 11839.4 [6825.7, 22520.8] | 97.6 [59.7, 100] | 99 [73, 100] | 86.5 |

Abbreviations: PK = pharmacokinetics; APW = alternative pathway activity by Wieslab assay; AUC = area under the concentration curve; Cmax = maximum concentration; Ctrough = trough concentration; BID = twice daily; QD = once daily; QID = four times daily; TID = three times daily.

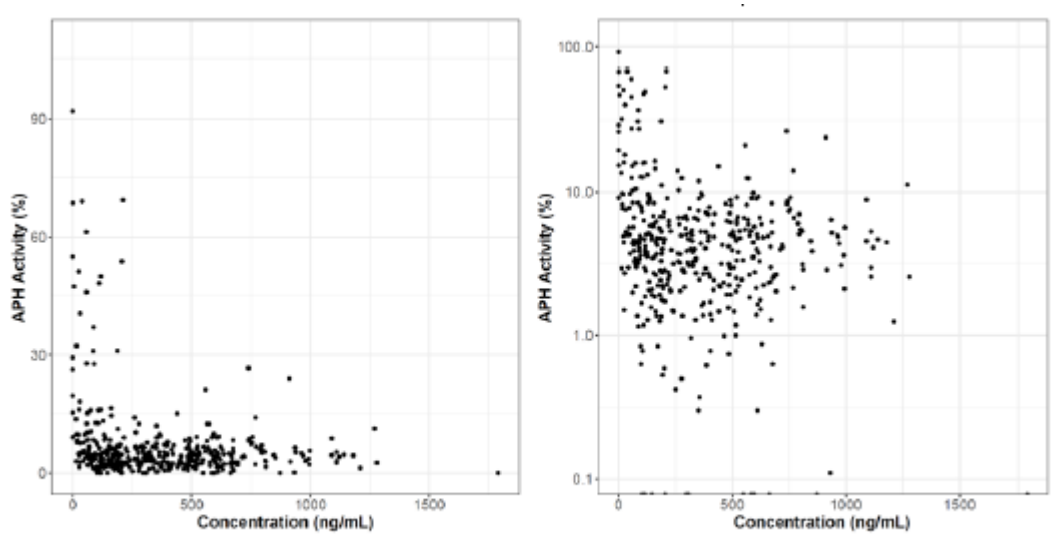
Notes: PK and APW values are reported as median [2.5 to 97.5%ile] of 1000 simulated subjects at steady state.

Source: pk.apw.sim.r

**PK-PD of APH**

The PK-PD dataset included 478 time-matched APH measurement – danicopan concentration values from 69 subjects with PNH in study ALXN2040-PNH-301. A total of 12 (2.5%) APH observations were BLQ, of which 9 were included in the dataset at a value of LLOQ/2 for implementation of the M6 method. An additional 3 BLQ samples that were the second consecutive BLQ samples in the same subject were excluded from the analysis dataset. The PKPD analysis dataset included 475 time-matched APH measurement – danicopan concentration values.

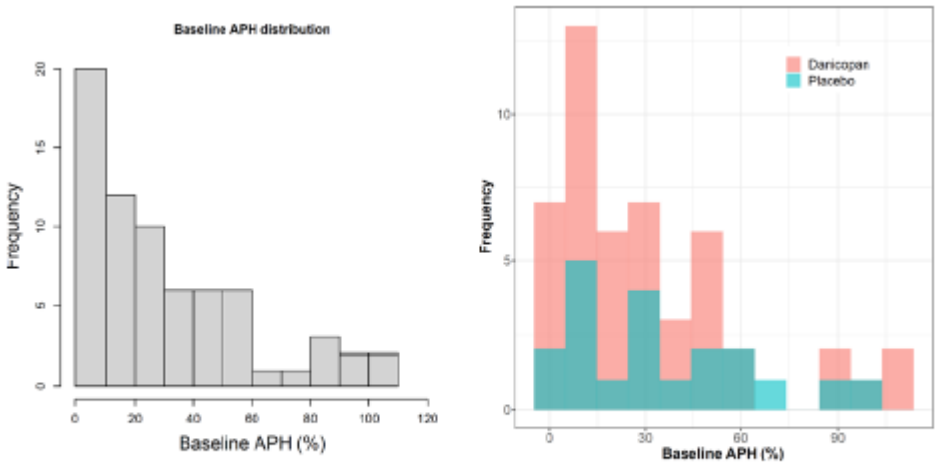
The figure below shows Cartesian and semi-log plots of individual APH activity versus danicopan observed concentration.




Abbreviations: APH = alternative pathway activity by hemolysis assay.
Source: 2022-09-26 APH PKPD data.v2.r

**Figure 17: APH versus Danicopan Observed Concentration**

The figure below shows the distribution of baseline APH in the overall study population and stratified by treatment group.




Abbreviations: APH = alternative pathway activity by hemolysis assay.
Source: 2022-09-26 APH PKPD data.v2.r

**Figure 18: Histogram of baseline APH**

Base APH Model

Based on exploratory evaluations, an $E_{max}$ model was considered to describe the relationship between danicopan concentrations and APH. The model had the form:

$$APH = APH_0 - (APH_0 - I_{max}) \times \frac{CONC}{(IC_{50}+CONC)} \qquad \text{Equation 4-1}$$

where APH0 is the baseline APH, $I_{max}$ is the minimum APH due to inhibition by danicopan and (APH0 – $I_{max}$) is the maximum APH inhibition achieved after treatment, CONC is the danicopan concentration, and IC50 is the danicopan concentration that produces half of the maximum inhibition of APH.

The model was estimated with imputation of the first BLQ by LLOQ/2 and removal of subsequent BLQ (M6 method), as described previously.

Covariate Effects

Candidate covariates were selected by screening covariates' correlation with ETAs of model parameters. All significant relationships ($p<0.05$) thus identified were introduced into a full APH model. These were weight, sex, East Asia and Factor D on APH0 and Japan on IC50. A stepwise deletion procedure removed covariates that were not significant ($p<0.05$) one at a time from the full model. After exclusion of these covariates, the resultant model, including weight and East Asian on APH0, was considered the final APH model.

Final APH Model

The final APH model parameter estimates are presented in Table 24.

**Table 24: Population Parameter Estimates for the Final APH Model**

| Parameter | Unit | Estimate | RSE (%) | Shrinkage (%) |
|---|---|---|---|---|
| $APH_0$ | % | 29.1 | 10.5 | |
| $IC_{50}$ | ng/mL | 12.0 | 33.4 | |
| Imax | % | 3.05 | 6.56 | |
| Weight on $APH_0$ | | 1.29 | 25.1 | |
| East Asian on $APH_0$ | | -0.460 | 25.8 | |
| **IIV (%BSV)** | | | | |
| $\omega^2$_BASE* | | 91.1 (9.5%) | 30.2 | 30.8 |
| $\omega^2$_$IC_{50}$# | | 5.26 (229%) | 36.5 | 27.1 |
| **Residual Error** | | | | |
| Proportional | % | 67.1 | 5.31 | 5.9 |

Abbreviations: APH = alternative pathway activity by hemolysis assay; $APH_0$ = baseline APH; BSV = between subject variability; $IC_{50}$ = danicopan concentration that produces half of maximum APH inhibition; IIV = interindividual variability; Imax = minimum APH due to inhibition by danicopan.
Notes: *additive IIV on $APH_0$, BSV is reported as a standard deviation in % APH units; #exponential IIV on $IC_{50}$, BSV is reported as % coefficient of variation. RSE calculated as standard error/estimate x 100.
Source: PD_run359.lst

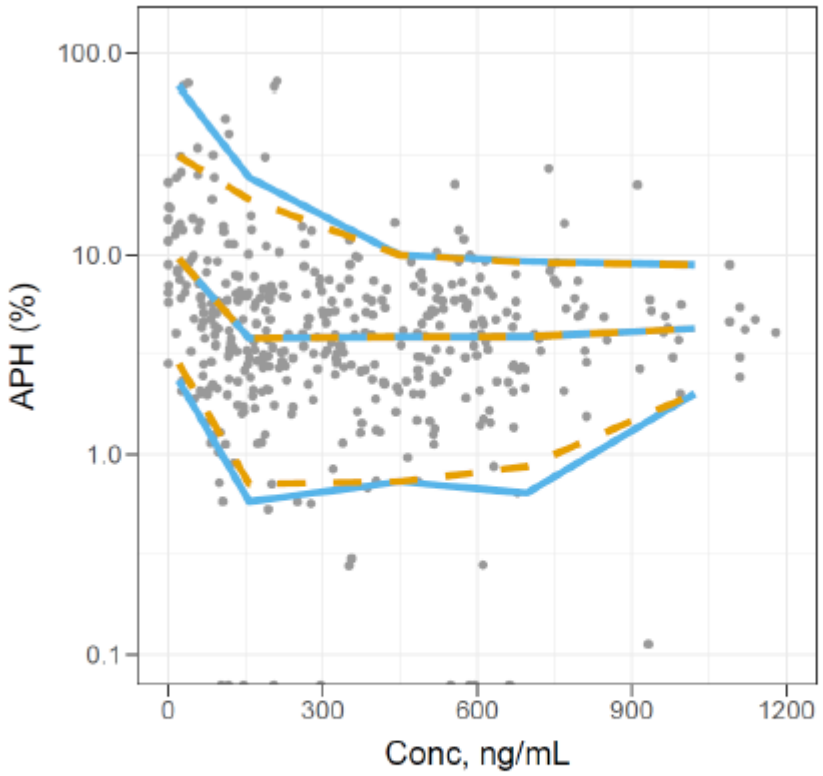
The final model parameters and covariate relationships are described in Equation 4-4

$$APH_{0i} = 29.1 \times \left(\frac{BWT_i}{69}\right)^{1.29} \times [1 - 0.460\ (if\ East\ Asian)]$$

$$APH_i = APH_{0i} - (APH_{0i} - 3.05) \times \frac{CONCi}{(12+CONCi)} \qquad \textbf{Equation 4-4}$$

where subscript i represents patient i, APH0 = estimated baseline APH, BWT = baseline body weight.

pcVPCs of overall APH results (Figure 19) show that the model adequately captured the central tendency and variability of data in subjects with PNH.

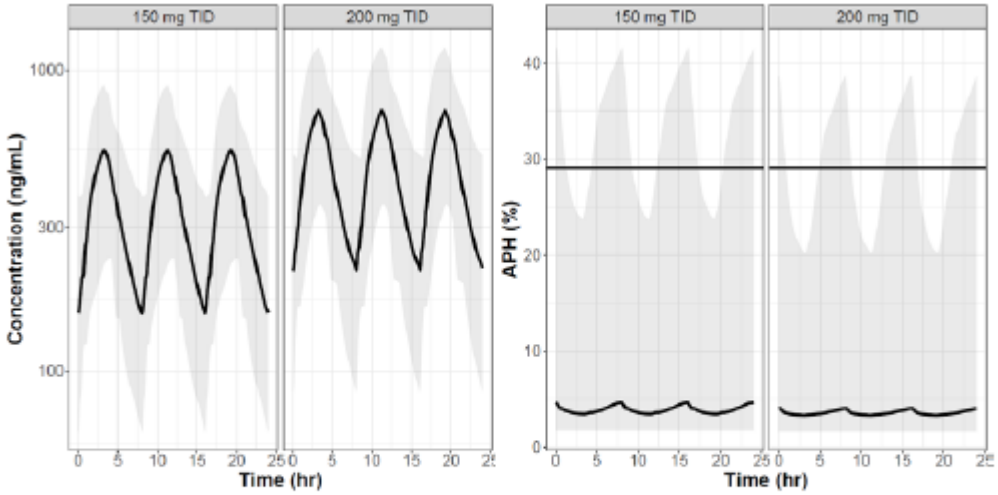



Abbreviations: APH = alternative pathway activity by hemolysis assay; Conc = danicopan concentration; pcVPC = prediction-corrected visual predictive check.
Notes: Grey dots are individual prediction-corrected values. Yellow dashed lines represent the 5th, 50th (median) and 95th percentiles of the observed APH over the range of danicopan concentrations. Solid blue lines represent the 5th, 50th (median) and 95th percentiles of the predictions from 1000 simulations.
Source: gof-v7.2.r

**Figure 19: pc-VPC for inal APH Model**

PK-PD Model Simulation for APH

Simulated PK and APH profiles are illustrated in Figure 20 for 150 mg and 200 mg TID. The simulations were done for the PNH population in Study ALXN2040-PNH-301 with danicopan tablet administered with standard meal. PK and APH model covariates, including baseline body weight, sex and subject of East Asian, were sampled from the population in Study ALXN2040-PNH-301. Post-hoc PK and APH model parameters were used in the simulation of interindividual variability. 1000 subjects were simulated by re-sampling of the covariates and post-hoc PK and APH model parameters to calculate the 95% predictive intervals.




Abbreviations: PK = pharmacokinetics; APH = alternative pathway activity by hemolysis assay; TID = three times daily.

Notes: Black lines are median and gray area are [2.5 to 97.5%ile] of 1000 simulated subjects at steady state. Solid horizontal line in the right panel indicate median baseline APH estimated. Observed baseline APH ranged from 0.56% to 109 % in study ALXN2040-PNH-301.

Source: pk.aph.sim.r

**Figure 20: Simulated steady state PK and APH for 150 mg and 200 TID regimens**

Summary of steady-state PK and APH measurements in PNH patients are provided in Table below. At a danicopan dose of 150 mg TID, the average APH inhibition was 80.4% for the duration of steady-state danicopan concentrations, and 77.5% inhibition at danicopan Ctrough. The inhibition rate was slightly higher at a dose of 200 mg TID, with average APH inhibition of 81.9% at steady-state and 79.9% at danicopan Ctrough. Both 150 mg TID and 200 mg TID regimens achieved a high and similar level of APH inhibition that was a plateau over the range of danicopan exposures achieved at these doses.

**Table 25: Simulated Steady State PK and APH Parameters for 150 mg and 200 mg TID Regimens**

| | PK | | | APH | | |
|---|---|---|---|---|---|---|
| Regimen | Cmax,ss (ng/mL) | Ctrough,ss (ng/mL) | AUC24h,ss (ng.hr/mL) | APH at trough (%) | % Inhibition from baseline at trough | % Average inhibition from baseline |
| 150 mg TID | 556 [237.5, 888.3] | 154.9 [63.2, 352.3] | 8055.1 [4033.1, 12885.8] | 4.7 [1.8, 41.5] | 77.5 [8.9, 100] | 80.4 [16.8, 100] |
| 200 mg TID | 718.6 [316.6, 1222.3] | 216.8 [84.3, 469.7] | 10904.6 [5377.5, 17181.1] | 4.0 [1.7, 38.6] | 79.9 [19.9, 100] | 81.9 [22.4, 100] |

Abbreviations: APH = alternative pathway activity by hemolysis assay; AUC24h,ss =steady state area under the curve over 24 h; Cmax,ss = steady state maximum plasma concentration; Ctrough,ss = steady state minimum (trough) plasma concentration; PK = pharmacokinetics; TID = three times daily.

Notes: PK and APH values are reported as median [2.5 to 97.5%ile] of 1000 simulated subjects at steady state.

Source: pk.aph.sim.r

***Secondary pharmacology***

**Study ACH471-013**

This Phase 1 SAD, randomised, double-blind, double-dummy, placebo-and positive-controlled, 2-arm, parallel TQT study was conducted to evaluate the effect of danicopan on the QT interval in healthy adult participants at dose levels of 400, 800, and 1200 mg (up to 6-fold compared with the therapeutic dose of 200 mg).

QTc effects of danicopan were compared with moxifloxacin. Moxifloxacin, a synthetic C-8-methoxy-fluoroquinolone antimicrobial agent active against Gram-negative and Gram-positive bacteria, prolongs

QT interval duration and is used as a positive control in most TQT studies to determine study sensitivity.

Participants were randomised into a treatment group and control group. Participants (N = 9) in the treatment group received all 3 doses of danicopan in a single ascending fashion over 3 periods (Treatment A, B, C). Participants randomised to the control group (N = 24) were further randomised to receive 1 of 2 treatment sequences (Treatment E, F, G or Treatment I, J, K).

All 33 participants who received at least 1 dose of the study intervention (danicopan, moxifloxacin, or matching placebo), had at least 1 valid Day 1 QT/QTc interval measurement at predose and postdose were included in the PK Analysis Population with a time-matched QTc/PK assessment and were included in the concentration-QT (C-QT) relationship analysis as per protocol.

Figure 21 illustrates the ddQTcF (change from Baseline in QTcF [corrected QT using Fridericia's formula] versus danicopan prediction line and 90% CI band from the final selected model. Dashed lines represent the upper 90% CI for ddQTcF at each geometric mean $C_{max}$ for each dose level tested. The estimated slope of baseline-adjusted QTcF (dQTcF) versus danicopan relationship was not statistically significant (p = 0.0569) and close to zero (0.0013) with a relatively narrow 95% CI: -0.0000, 0.0027.

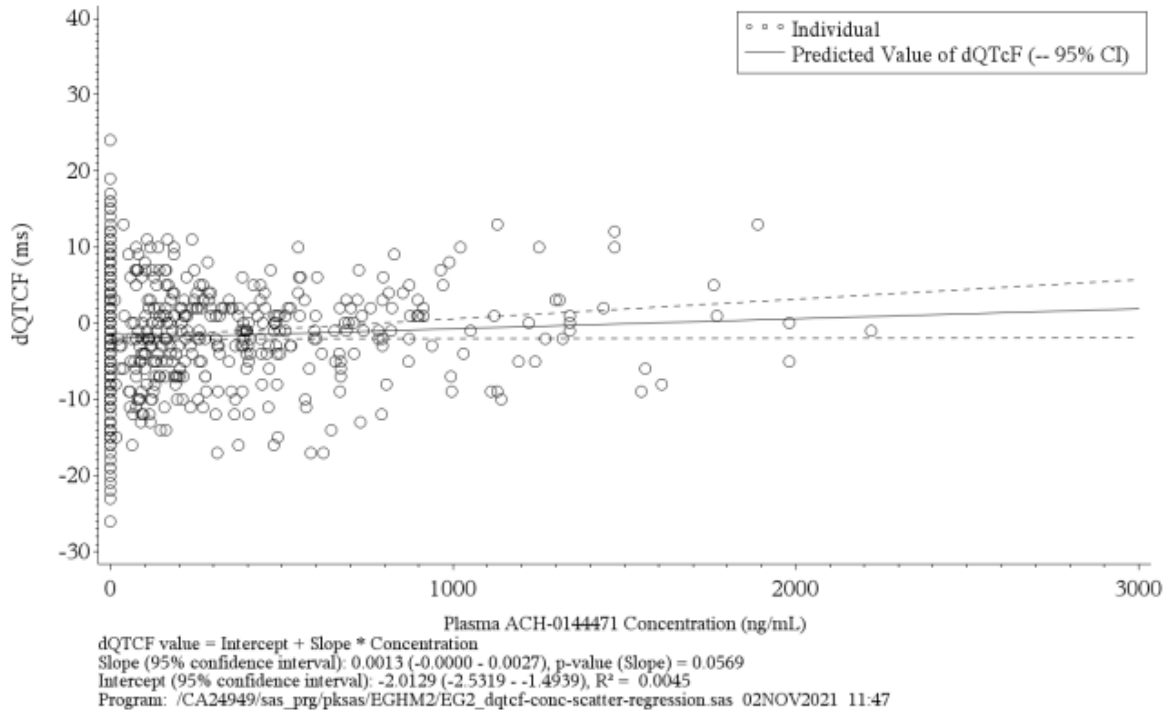



**Figure 21: Change From Baseline in QTcF (dQTcF) Versus Time-Matched Plasma ACH-0144471 Concentrations (Scatterplot, ACH-0144471) (Placebo Included) (C-QT Population)**

The model-predicted ddQTcF and 90% CI at geometric mean $C_{max}$ for danicopan are provided in ACH471-013 CSR (not shown here). The predicted values for ddQTcF at geometric mean $C_{max}$ for each treatment and dose level were minimal, ranging from approximately 0.837 to 1.402 msec. The highest upper bound of 2-sided 90% CI for the predicted maximum ddQTcF at geometric mean $C_{max}$ was 3.507 msec for danicopan 1200 mg. At geometric mean $C_{max}$ of all dose levels tested, the upper bound of 2-sided 90% CI estimate was significantly below the regulatory threshold of concern of 10 msec. Therefore, danicopan does not cause clinically relevant QTc prolongation over the dose range tested (400 to 1200 mg).

**Table 26: Model predicted placebo-corrected change from baseline in QTcF (ddQTcF) and 90% CI at geometric mean $C_{max}$ of ACH-0144471 by Treatment (C-QT Population)**

| Treatment | Geometric Mean Cmax* (ng/mL) | Predicted ddQTcF (ms) | 90% Confidence Interval (ms) |
|---|---|---|---|
| A | 535.2 | 0.837 | -1.088 - 2.761 |
| B | 869.8 | 1.222 | -0.801 - 3.245 |
| C | 1027 | 1.402 | -0.702 - 3.507 |

Predicted values of dQTcF correlated well with observed values. Quantiles of plasma danicopan overlaid upon the slope with 90% CI band predicted by the final selected model demonstrates that the model was well specified (Figure 22).

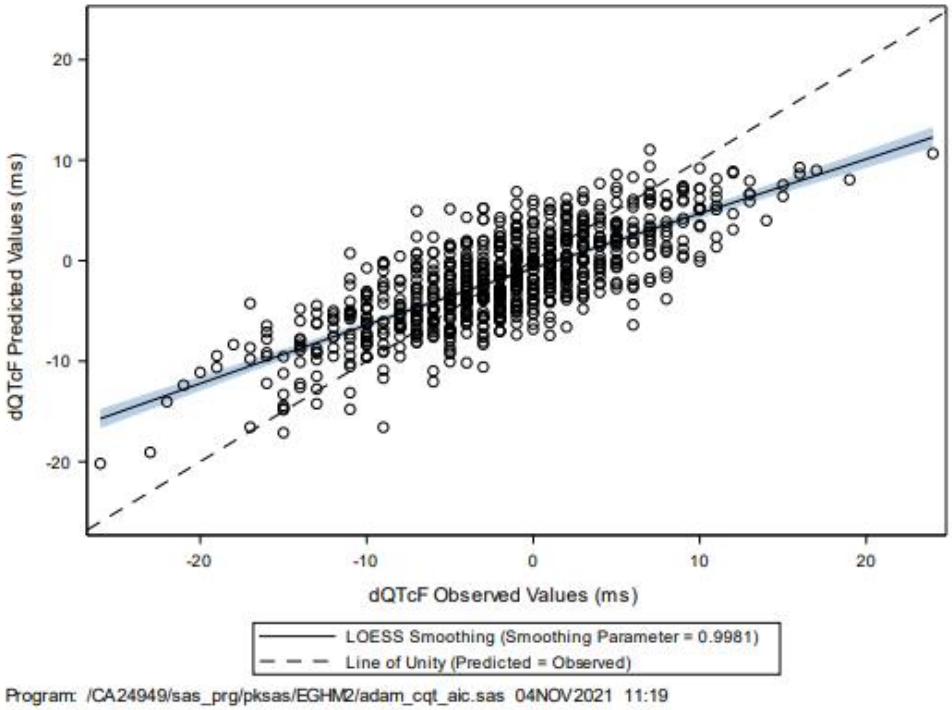
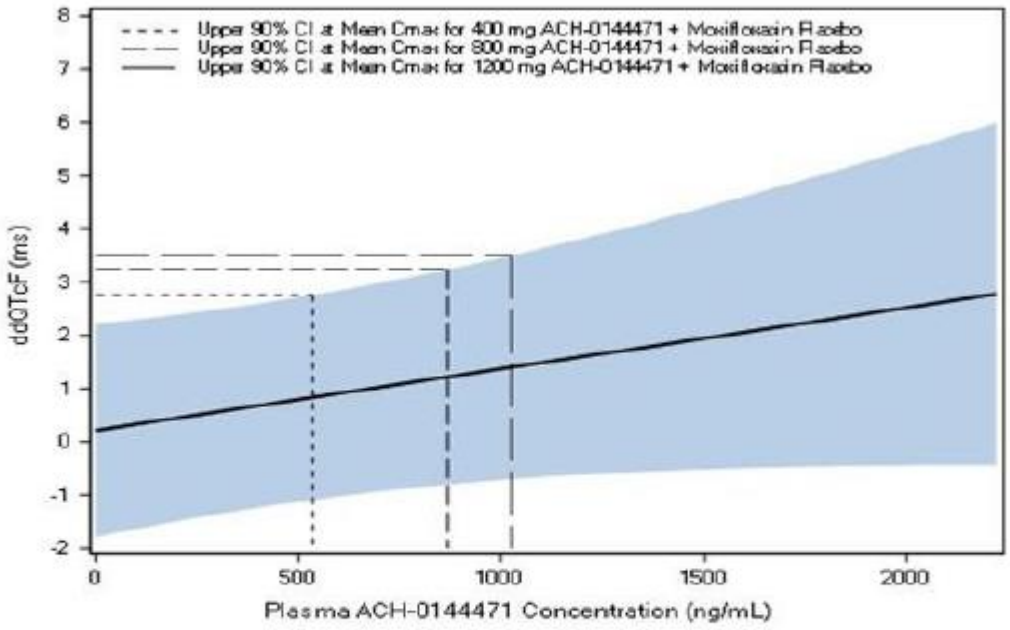
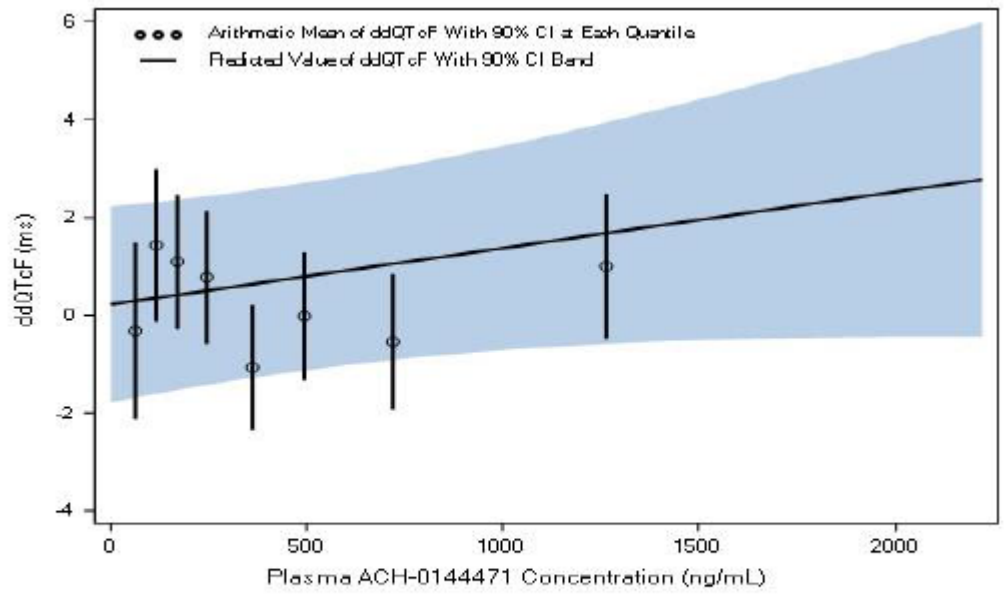



**Figure 22: Model Diagnostic: dQTcF predicted values versus observed values with LOESS smoothing line with 95% confidence interval and line of unity (ACH-0144471) (C-QT opulation)**




Note: Predicted line and 90% confidence interval are from the final linear model.
Abbreviations: ACH-0144471 = danicopan; CI = confidence interval; $C_{max}$ = maximum observed concentration; C-QT = concentration QT; ddQTcF = change from baseline in QTcF; QTcF = corrected QT interval using Fridericia's formula
Source: ACH471-013 CSR Addendum Figure 14.2.6.36

**Figure 23: Model Predicted (90% CI) Placebo-Corrected Change from Baseline in QTcF (ddQTcF) Versus Time-Matched Plasma Danicopan Concentrations (C-QT Population) (Study ACH471-013)**




Predicted line and 90% confidence interval are from the final linear model.
Abbreviations: ACH-0144471 = danicopan; CI = confidence interval; C-QT = concentration QT; ddQTcF = change from baseline in QTcF; QTcF = corrected QT interval using Fridericia's formula
Source: ACH471-013 CSR Addendum Figure 14.2.6.34

**Figure 24: Quantiles of plasma danicopan concentration and placebo-corrected change from baseline in QTcF (ddQTcF) overlaid with slope of final model (C-QT Population) (Study ACH471-013)**

***Relationship between plasma concentration and effect***

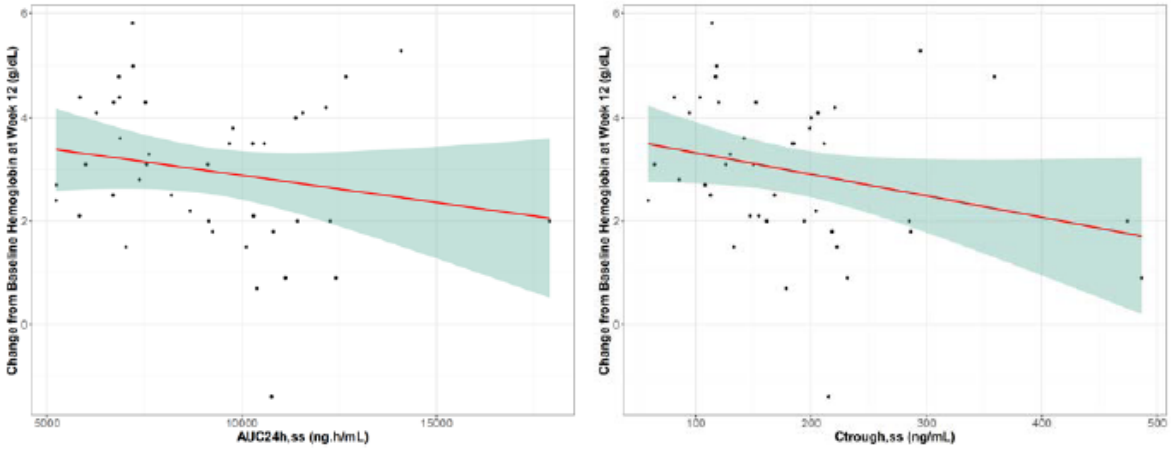
**Exposure Response Analysis of Efficacy Endpoints**

The efficacy dataset included data from 63 subjects from study ALXN2040-PNH-301. Of these subjects, 42 received danicopan and 21 received placebo during the 12-week double blind period (Period 1) of the study.

A total of 8 out of 42 subjects assigned to received danicopan were escalated to 200 mg TID after week 6.

Change in Haemoglobin Relative to Baseline at Week 12

The relationship between change in Hgb from baseline at Week 12 and danicopan exposure was described using a linear regression model (Figure 25).




Abbreviations: AUC24h,ss = area under the danicopan plasma concentration vs. time curve over a period of 24 hr at Week 12, Ctrough,ss = minimum danicopan concentration at Week 12.
Notes: Red line is a linear regression; shaded region is the 95% confidence interval for the regression line.
Source: eeanalysis.r

**Figure 25: Relationship between Change in Haemoglobin from Baseline at Week 12 and Danicopan Exposure**

No significant relationship between change in Hgb from baseline at Week 12 and danicopan exposure was observed in this analysis.

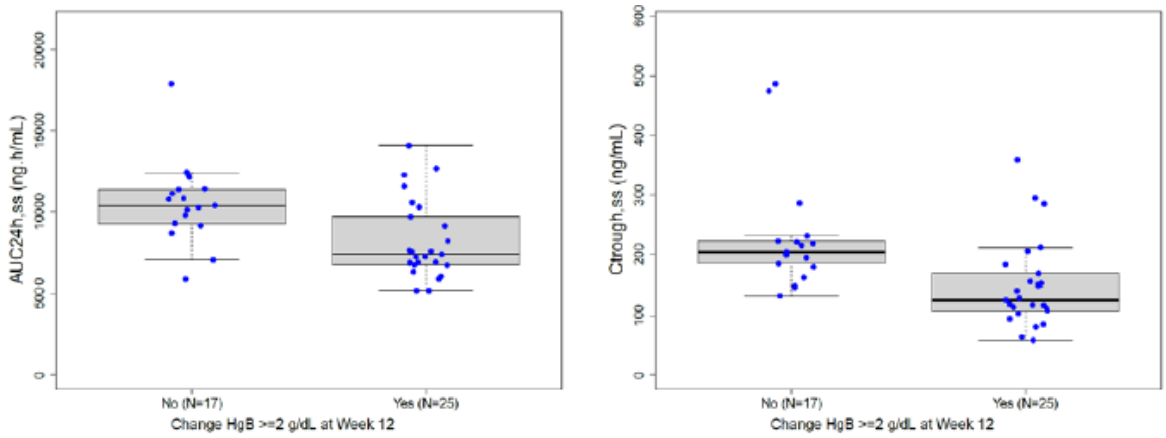
**Table 27: Change in Haemoglobin from Baseline at Week 12 Parameter Estimates**

| Exposure Metric | Parameter | Estimate | SE | P-value |
|---|---|---|---|---|
| AUC24h,ss (ng.h/mL) | Intercept | 3.94 | 0.791 | $1.28 \times 10^{-5}$ |
| | Slope | $-1.05 \times 10^{-4}$ | $8.31 \times 10^{-5}$ | 0.213 |
| $C_{trough,ss}$ (ng/mL) | Intercept | 3.74 | 0.483 | $1.81 \times 10^{-9}$ |
| | Slope | -0.00417 | 0.00236 | 0.0847 |

Abbreviations: AUC24h,ss = area under the danicopan plasma concentration vs. time curve over a period of 24 hr at Week 12, Ctrough,ss = minimum danicopan concentration at Week 12.
Source: eeanalysis.r

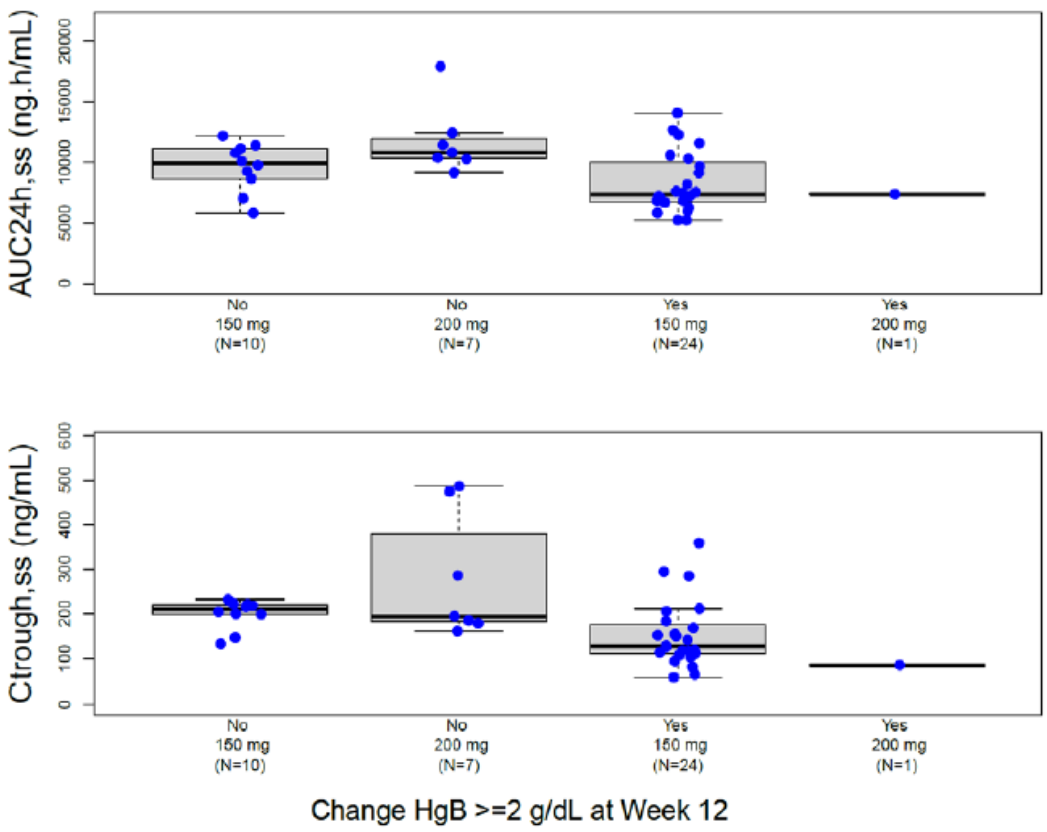
Proportion of Subjects with Hgb Increase of ≥ 2 g/dL at Week 12

Figure 26 shows boxplots of danicopan exposures grouped by haemoglobin change from baseline in the treated cohort. Boxplots stratified by response and the dose prior to the Week 12 assessment in the treated cohort are shown in Figure 27. Hgb responses summarised by exposure quartiles, and further stratified by steady state dose before the Week 12 assessment are shown in Table 28.




Abbreviations: AUC24h,ss = area under the danicopan plasma concentration vs. time curve over a period of 24 hr at Week 12, Ctrough,ss = minimum danicopan concentration at Week 12; Hgb = hemoglobin.
Note: Blue circles represent individual observations.
Source: eeanalysis.r

**Figure 26: Boxplots of Danicopan Exposures Grouped by Change in Haemoglobin Category**




Abbreviations: AUC24h,ss = area under the danicopan plasma concentration vs. time curve over a period of 24 hr at Week 12; Ctrough,ss = minimum danicopan concentration at Week 12; N = number of subjects.
Source: eeanalysis.r

**Figure 27: Boxplots of Danicopan Exposures Grouped by Change in Haemoglobin Category and Dose Prior to The Week 12 Assessment**

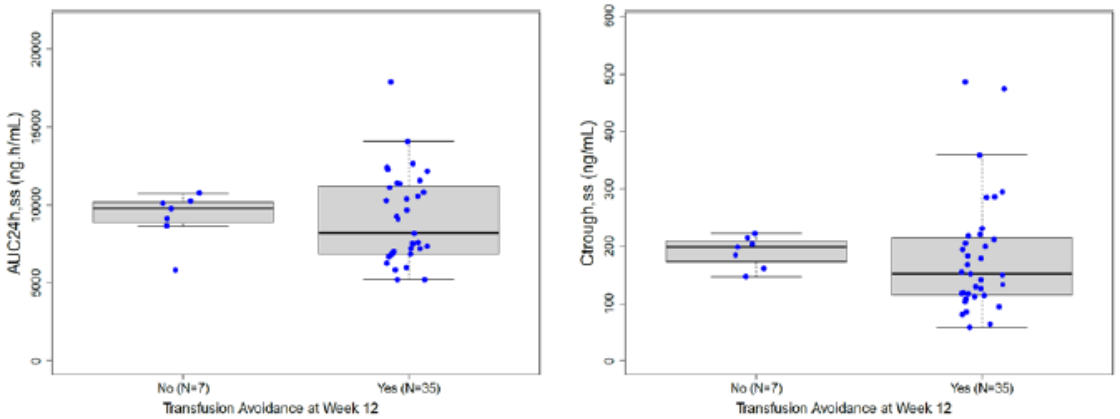
**Table 28: Summary of Hgb Increase ≥ 2 g/dL to Week 12**

| | | AUC24h,ss | | | |
|---|---|---|---|---|---|
| | Placebo | Q1 (5320 - 6880 ng.h/mL) | Q2 (7020 – 9130 ng.h/mL) | Q3 (9150 – 10800 ng.h/mL) | Q4 (10800 – 17900 ng.h/mL) |
| **All Subjects** | | | | | |
| N | 21 | 11 | 10 | 10 | 11 |
| No | 21 (100%) | 1 (9.1%) | 2 (20.0%) | 7 (70.0%) | 7 (63.6%) |
| Yes | 0 (0%) | 10 (90.9%) | 8 (80.0%) | 3 (30.0%) | 4 (36.4%) |
| **Week 12 dose= 150 mg** | | | | | |
| N | - | 11 | 9 | 7 | 7 |
| No | - | 1 (9.1%) | 2 (22.2%) | 4 (57.1%) | 3 (42.9%) |
| Yes | - | 10 (90.9%) | 7 (77.8%) | 3 (42.9%) | 4 (57.1%) |
| **Week 12 dose= 200 mg** | | | | | |
| N | - | 0 | 1 | 3 | 4 |
| No | - | 0 | 0 (0%) | 3 (100%) | 4 (100%) |
| Yes | - | 0 | 1 (100%) | 0 (0%) | 0 (0%) |

Abbreviations: Q = quartile.
Notes: Values are count (%).
Source: eeanalysis.r

Transfusion Avoidance at Week 12

Figure 28 shows boxplots of danicopan exposures grouped by transfusion avoidance in the treated cohort. Exposures largely overlapped between groups who did and did not experience transfusion avoidance and no difference was observed.




Abbreviations: AUC24h,ss = area under the danicopan plasma concentration vs. time curve over a period of 24 hr at Week 12, Ctrough,ss = minimum danicopan concentration at Week 12.
Note: Blue circles represent individual observations.
Source: eeanalysis.r

**Figure 28: Boxplots of Danicopan Exposures Grouped by Transfusion Avoidance Category**

Transfusion avoidance summarised by exposure quartiles, and further stratified by steady state dose before the Week 12 assessment is summarised in Table below.

**Table 29: Summary of Transfusion Avoidance**

| | | AUC24h,ss | | | |
|---|---|---|---|---|---|
| | Placebo | Q1 (5320 - 6880 ng.h/mL) | Q2 (7020 – 9130 ng.h/mL) | Q3 (9150 – 10800 ng.h/mL) | Q4 (10800 – 17900 ng.h/mL) |
| **All Subjects** | | | | | |
| N | 21 | 11 | 10 | 10 | 11 |
| No | 13 (61.9%) | 1 (9.1%) | 1 (10.0%) | 5 (50.0%) | 0 (0%) |
| Yes | 8 (38.1%) | 10 (90.9%) | 9 (90.0%) | 5 (50.0%) | 11 (100%) |
| **Week 12 dose= 150 mg** | | | | | |
| N | - | 11 | 9 | 7 | 7 |
| No | - | 1 (9.1%) | 1 (11.1%) | 3 (42.9%) | 0 (0%) |
| Yes | - | 10 (90.9%) | 8 (88.9%) | 4 (57.1%) | 7 (100%) |
| **Week 12 dose= 200 mg** | | | | | |
| N | - | 0 | 1 | 3 | 4 |
| No | - | 0 | 0 (0%) | 2 (66.7%) | 0 (0%) |
| Yes | - | 0 | 1 (100%) | 1 (33.3%) | 4 (100%) |

Abbreviations: Q = quartile.
Notes: Values are count (%).
Source: eeanalysis.r

**Exposure Response Analysis of Safety Endpoints**

The safety dataset included data from 73 subjects from study ALXN2040-PNH-301 and only the safety events up to the Week 12 assessment (Period 1) were included in this ER analysis. Of these subjects, 49 received danicopan and 24 received placebo.

Safety endpoints included in the descriptive exposure-response analysis are summarised by treatment cohort in Table 30.

**Table 30: Summary of AEs by Treatment Cohort**

| | Danicopan (N=49) | Placebo (N=24) | Overall (N=73) |
|---|---|---|---|
| Any SAE | 2 (4.1%) | 1 (4.2%) | 3 (4.1%) |
| Arthralgia | 4 (8.2%) | 2 (8.3%) | 6 (8.2%) |
| Diarrhoea | 4 (8.2%) | 3 (12.5%) | 7 (9.6%) |
| Headache | 5 (10.2%) | 1 (4.2%) | 6 (8.2%) |
| Hypertension | 3 (6.1%) | 1 (4.2%) | 4 (5.5%) |
| Elevated liver enzymes | 6 (12.2%) | 2 (8.3%) | 8 (11%) |
| Meningococcal Infection | 0 (0%) | 0 (0%) | 0 (0%) |
| Nausea | 4 (8.2%) | 2 (8.3%) | 6 (8.2%) |
| Pyrexia | 3 (6.1%) | 0 (0%) | 3 (4.1%) |
| Vomiting | 3 (6.1%) | 0 (0%) | 3 (4.1%) |

Abbreviations: AD = adverse event; N= number of subjects; SAE = serious adverse event.
Notes: Values are counts and the percent of subjects in the treatment group.
Source: es.analysis.r

Summaries of safety endpoints by quartiles of AUC24h,ss and $C_{max}$,ss are shown in Table 31 and Table 32, respectively.

**Table 31: Summary of TEAEs Greater Than or Equal to 5%* by Quartiles of AUC24h,ss**

| | | AUC24h,ss | | | |
|---|---|---|---|---|---|
| | Placebo (N=24) | Q1 (3305 – 6876 ng.h/mL) (N=13) | Q2 (7021 – 9150 ng.h/mL) (N=12) | Q3 (9250 – 11125 ng.h/mL) (N=12) | Q4 (11249 – 17906 ng.h/mL) (N=12) |
| Any SAE | 1 (4.2%) [-3.8, 12.2%] | 0 (0%) [0, 0%] | 2 (16.7%) [-4.4, 37.8%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] |
| Arthralgia | 2 (8.3%) [-2.7, 19.4%] | 0 (0%) [0, 0%] | 1 (8.3%) [-7.3, 24%] | 2 (16.7%) [-4.4, 37.8%] | 1 (8.3%) [-7.3, 24%] |
| Diarrhoea | 3 (12.5%) [-0.7, 25.7%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 3 (25%) [0.5, 49.5%] | 1 (8.3%) [-7.3, 24%] |
| Headache | 1 (4.2%) [-3.8, 12.2%] | 1 (7.7%) [-6.8, 22.2%] | 1 (8.3%) [-7.3, 24%] | 1 (8.3%) [-7.3, 24%] | 2 (16.7%) [-4.4, 37.8%] |
| Hypertension | 1 (4.2%) [-3.8, 12.2%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 3 (25%) [0.5, 49.5%] |
| Elevated liver enzymes | 2 (8.3%) [-2.7, 19.4%] | 1 (7.7%) [-6.8, 22.2%] | 2 (16.7%) [-4.4, 37.8%] | 2 (16.7%) [-4.4, 37.8%] | 1 (8.3%) [-7.3, 24%] |
| Meningococcal Infection | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] |
| Nausea | 2 (8.3%) [-2.7, 19.4%] | 0 (0%) [0, 0%] | 1 (8.3%) [-7.3, 24%] | 2 (16.7%) [-4.4, 37.8%] | 1 (8.3%) [-7.3, 24%] |
| Pyrexia | 0 (0%) [0, 0%] | 1 (7.7%) [-6.8, 22.2%] | 1 (8.3%) [-7.3, 24%] | 0 (0%) [0, 0%] | 1 (8.3%) [-7.3, 24%] |
| Vomiting | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 2 (16.7%) [-4.4, 37.8%] | 0 (0%) [0, 0%] | 1 (8.3%) [-7.3, 24%] |

Abbreviations: AE = adverse event; N= number of subjects; Q = quartile; SAE = serious adverse event.
Notes: Values are counts (%) [95% confidence interval]. * TEAEs >=5% as well as prespecified AE Meningococcal Infection were included
Source: es.analysis.r

**Table 32: Summary of TEAEs Greater Than or Equal to 5%* by Quartiles of $C_{max,ss}$**

| | | Cmax,ss | | | |
|---|---|---|---|---|---|
| | Placebo (N=24) | Q1 (151 – 478 ng/mL) (N=13) | Q2 (490 – 557 ng/mL) (N=12) | Q3 (595 – 747 ng/mL) (N=12) | Q4 (748 – 1017 ng/mL) (N=12) |
| Any SAE | 1 (4.2%) [-3.8, 12.2%] | 1 (7.7%) [-6.8, 22.2%] | 1 (8.3%) [-7.3, 24%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] |
| Arthralgia | 2 (8.3%) [-2.7, 19.4%] | 1 (7.7%) [-6.8, 22.2%] | 0 (0%) [0, 0%] | 2 (16.7%) [-4.4, 37.8%] | 1 (8.3%) [-7.3, 24%] |
| Diarrhoea | 3 (12.5%) [-0.7, 25.7%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 3 (25%) [0.5, 49.5%] | 1 (8.3%) [-7.3, 24%] |
| Headache | 1 (4.2%) [-3.8, 12.2%] | 2 (15.4%) [-4.2, 35%] | 1 (8.3%) [-7.3, 24%] | 1 (8.3%) [-7.3, 24%] | 1 (8.3%) [-7.3, 24%] |
| Hypertension | 1 (4.2%) [-3.8, 12.2%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 3 (25%) [0.5, 49.5%] |
| Elevated liver enzymes | 2 (8.3%) [-2.7, 19.4%] | 1 (7.7%) [-6.8, 22.2%] | 2 (16.7%) [-4.4, 37.8%] | 3 (25%) [0.5, 49.5%] | 0 (0%) [0, 0%] |
| Meningococcal Infection | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] |
| Nausea | 2 (8.3%) [-2.7, 19.4%] | 0 (0%) [0, 0%] | 1 (8.3%) [-7.3, 24%] | 2 (16.7%) [-4.4, 37.8%] | 1 (8.3%) [-7.3, 24%] |
| Pyrexia | 0 (0%) [0, 0%] | 1 (7.7%) [-6.8, 22.2%] | 1 (8.3%) [-7.3, 24%] | 0 (0%) [0, 0%] | 1 (8.3%) [-7.3, 24%] |
| Vomiting | 0 (0%) [0, 0%] | 0 (0%) [0, 0%] | 2 (16.7%) [-4.4, 37.8%] | 0 (0%) [0, 0%] | 1 (8.3%) [-7.3, 24%] |

Abbreviations: AE = adverse event; N= number of subjects; Q = quartile; SAE = serious adverse event.
Notes: Values are counts and the percent of subjects in the treatment group. * TEAEs >=5% as well as prespecified AE Meningococcal Infection were included
Source: es.analysis.r

## 2.6.3. Discussion on clinical pharmacology

**Pharmacokinetics**

Analytical methods

Overall, method validation for the analytical quantification of danicopan and bioanalytical sample analysis for all studies was carried out successfully according to the EMA Guideline on bioanalytical method validation (2011) and ICH Guideline M10.

Bioequivalence

Danicopan is intended to be commercialised in 50- and 100-mg tablet forms. however a formal bioequivalence study between the 50-mg and the 100-mg tablet formulation is not required in principle, as both formulations intended to be commercialised were included in the pivotal clinical trial.

The bioavailability of the 100 mg strength was described in fasted vs fed conditions and it is acknowledged that both strengths have the same qualitative composition and that the composition is quantitatively proportional. However, taking into account that PK dose-proportionality could not be established for danicopan in studies ACH471-001 and ACH471-002, and that the pharmaceutical development presented in Module 3 shows that the dissolution profile for both strengths is not similar, it was uncertain whether the 50 mg dose had the same bioavailability as the 100 mg dose. The applicant provided further justification on this point, and it was concluded that the dissolution similarity demonstrated for the 50 and 100 mg strengths at 75 rpm without surfactant and the QC method are considered sufficient.

Absorption

Danicopan has low solubility, and the food intake increases its absorption, most probably due the solubilisation effect of the bile secreted after food intake. Danicopan is rapidly absorbed after oral dosing, with mean time to maximum observed concentration occurring at about 3 hours post dose. Over the dose range of 200 mg to 800 mg, $C_{max}$ increased in a less than dose-proportional manner, likely due to solubility-limited absorption.

The absorption of danicopan and whether it could be considered complete based on the entities (parent or metabolite) and type of metabolites (oxidative, conjugative, hydrolysed or reduced) found in the faeces, was discussed. Available mass-balance and metabolite characterisation data indicated that danicopan is completely absorbed. However, permeability classification was not possible since the hydrolysis of danicopan may occur before its absorption in the gastrointestinal lumen as well as its reduction by bacteria. Limited data provided suggests that the metabolites ACH-0144709 and ACH-0145071/ACH-0145072 are predominantly formed after absorption.

Danicopan is highly permeable and a P-gp substrate *in vitro* but with low efflux ratio. The oral exposure of danicopan does not appear to be affected by P-gp efflux in the gastrointestinal tract. Danicopan is not a substrate of BCRP, OATP1B1, or OATP1B3.

Influence of food

In a dedicated formal Study ACH471-016, the effect of a high fat/high calorie breakfast on danicopan PK was investigated in 17 healthy volunteers who were administered a single oral dose of 200 mg danicopan (2 *100 mg tablets) in the fasted and the fed states. PK results indicated that administration of a high fat breakfast increased moderately geometric mean AUC0-inf and AUC0-t by ~25%, while almost doubling the $C_{max}$ (increase of 93%). However, food had no significant effect on median $T_{max}$, with values of 3 and 2.5 hours under fed and fasted conditions respectively (see SmPC section 4.2 and 5.2).

The increase in danicopan exposure after a high fat breakfast for the 200 mg strength is lower than the increase observed in study ACH471-006, where 800 mg of danicopan were administered. It seems that the food-effect for danicopan is dose dependent, and that the higher the dose, the higher the increase in danicopan exposure after a moderate-fat meal (non-linear). In addition, it is noted that when danicopan is administered after a moderate fat-meal, the increase in danicopan exposure is lower compared to the increase observed with a high-fat meal.

According to the non-compartmental analysis of the PK parameters, it is observed that the first order elimination rate constant is very similar between fed and fasted state, so it can be agreed that the impact of food is related to a change in the bioavailable fraction of the drug. Statistical analysis suggests a high impact on $C_{max}$ when danicopan is administered with food.

Danicopan is no longer recommended to be administered in fasted state and the current recommendation is to be administered in fed state conditions, as in the Phase 3 study. The results of the AUC24h,ss and Ctrough,ss over the efficacy outcomes at different weeks after treatment initiation shows a flat relationship.

Two patients participated in Study ACH471-016 have undergone GIT surgery (appendectomy, inguinal hernia repair) in their recent medical history. All the patients experienced the abovementioned procedures have not suffered from any of the complications originated from the surgical interventions, therefore have not fulfilled the exclusion criteria of Study ACH471-016.

Distribution

Danicopan is highly bound to human plasma proteins (91.5% to 94.3%) and is mainly distributed in plasma with a ratio of whole blood to plasma mean $AUC_{0-\infty}$ of 0.545. Danicopan plasma concentrations appeared to decline in a biphasic manner after $T_{max}$ - this is compatible with a two-compartment PK model. The mean half-life of total danicopan and the half-life of danicopan in plasma and blood from the non-compartmental analysis of 14C radiolabel observations could be biased due to the impact of samples below the limit of quantification. In this regard, information of danicopan disposition on the SmPC was based on the results of the population PK model. The estimated oral apparent volume of distribution for a 75 kg person using the population-PK model was 168 L for Vc/F and 234 L for Vp/F (402 L total), suggesting a moderate distribution of danicopan to peripheral tissue.

Blood/Plasma AUC ratio was 0.545, a value lower than 1, indicating reduced penetration of danicopan into red blood cells. The free fraction of protein binding in human plasma of danicopan is from 5.7% to 8.5%.

Metabolism

Danicopan undergoes an extensive metabolism after oral dosing via non-CYP-mediated pathways (ie.: oxidation, reduction and hydrolysis). On the basis of human 14C ADME study, hydrolysis appeared to be major pathway of elimination. CYP-mediated pathways are minimally involved in metabolism of danicopan.

Elimination

Danicopan is mainly excreted through faeces (69.2%) and in a minor extent through urine (24.8%). The mass balance study recovered 94.0% (range: 91.0% to 97.2%) of danicopan from the excreta over 216 hour post-dose. Therefore, the results show an acceptable recovery for danicopan, in accordance with the EMA guidance. On the other hand, although the majority route is through the faeces, excretion via urine represents about a quarter of the excreted drug, so it is important to consider renal function as a relevant route of excretion for danicopan.

The metabolic pathways of danicopan have been properly characterised through the mass balance study after a single oral dose of 151 to 154 mg of danicopan, provided in a total of 2 liquid-filled capsules (LFCs) containing a total of approximately 100 µCi of $^{14}C$ radiolabel compound.

From the results of the mass balance study, it can be seen that danicopan is mainly metabolised to different metabolites, the unchanged portion of danicopan being <1% and <4% via the kidneys and faeces, respectively. Therefore, danicopan presents a high degree of metabolisation by enzymatic route.

The major metabolites identified were M8 and the isomeric mixture M5 that account of approximately 53% and 11% of total radioactive exposure (AUC 0.5-4h) in plasma respectively. The rest of the metabolites account for 1 to 5 % of total radioactivity exposure.

Dose proportionality and time dependency

The dose proportionality study has been performed in two phases: single dose regimen (Study ACH471-001) and multiple dose regimen (ACH471-002).

Based on PK data from healthy volunteers, a less than proportional increase over the dose range tested (200 to 1200 mg) for both $C_{max}$ and AUC was observed (Study ACH471-001), where only PK information after 200, 600 and 1200 mg was available following single dose administration. These results are in line with those obtained in the food effect study, where an evident dose-dependent impact of food on danicopan exposure was observed.

Study ACH471-002 includes the dose proportionality assessment after multiple dose regimen of 200, 500 and 800 mg. The results show comparable $C_{max}$ and AUC when normalised between 200 and 800 mg (dose proportional), but less than proportional increase of $C_{max}$ and AUC when 500 mg were administered. In addition, individual $C_{max}$ levels were more variable when 800 mg were administered compared to 200 mg, possibly due to the different solubilisation of danicopan in the GI tract at the highest dose (800 mg).

The less than proportional effect observed after single dose regimen (Study ACH471-001) could be more informative, since the system is not equilibrated after repeated drug administration, despite the accumulation is low (Ratio <2). On the other hand, the explanation provided by the MAH related to a low number of healthy volunteers per study is insufficient, since each one consists of >6 individuals per dose level. In addition, due to the numerous parameters and covariates included in the population PK model for characterizing the absorption phase and the relevant food effect related to drug solubility, there are uncertainties about the presence of mechanisms involved in the absorption process that could explain this effect. Section 5.2 of the SmPC was updated to reflect that "Over the dose range of 200 mg to 800 mg, $C_{max}$ increased in a less than dose-proportional manner, likely due to solubility-limited absorption."

In Study ACH471-001, less than dose proportionality is observed especially in $C_{max}$ and primarily at the highest dose (1200 mg). The Applicant states that Danicopan is a BCS 2 compound and a dose-dependent or solubility-limited absorption is expected. The dose-normalised $C_{max}$ at 200 mg Day 1 is 4.33, whereas the $C_{max}$/D ratio at 500 and 800 mg were 2.94 and 2.41. This tendency remains at day 7 and day 14, although a more similar $C_{max}$/D at 800 mg vs 200 mg is observed at day 14. Overall, the results suggest a less than proportional increase of $C_{max}$ over the dose range evaluated at single and multiple dose regimens.

Based on the results from phase 1 study ACH471-002 in healthy volunteers, accumulation ratios for $C_{max}$ and AUCtau at steady state (day 7 and day 14) ranged from 0.92 to 1.03 in cohort 1 (200 mg bid) and cohot 4 (75 mg tid). In cohort 2 (500 mg bid) and 3 (800 mg bid), accumulation ratios ranged from 1.16 to 1.77 for $C_{max}$ and 1.24 to 1.53 for AUCtau. The accumulation ratios of danicopan upon multiple dosing increased with increasing dose, but were low to moderate (Racc $\leq$ 2 for both AUCtau and $C_{max}$) at steady-state. According to the results, no time-dependency effect is observed in the exposure of danicopan.

Pharmacokinetics in target population

The Applicant has pooled PK longitudinal data from several (n=14) studies in healthy volunteers and patients using tablets and LFC formulations, at single and multiple dose regimens in fed and fasted state. First, a population PK model has been proposed using PK data from Phase I and Phase 2 studies. Then, the established population PK model was updated to characterise jointly the PK evidence collected in the Phase 3 trial (ALXN2040-PNH-301 study). The overall model development strategy, data management and use of BLQ observations (M1 method) are endorsed.

The base population PK model incorporates separated absorption parameters for LFC and tablet formulations, which may be reasonable at that level. Despite it represents the base population PK model, several covariates were included, such as a dose effect on F and food effect on F and D1 together with allometric relationship on disposition parameters (CL, Vc, Q and Vp). PK parameters were precisely estimated based on the RSE values (<30-40%). Moderate-to-high interindividual variability has been incorporated on several PK parameters (CL, Vc, Vp, Ka and D1). Eta-shrinkage were low, except for Ka (49%).

The final estimates of the parameters of the final population PK model, excluding or including the Phase 3 study, are very similar between both final population PK models. This suggests that there is no

different PK behaviour between the populations of the Phase I and II studies and the Phase III population, as expected. Furthermore, both final models present the same inter-individual random and covariate effects.

A zero-order release followed by first order absorption into the central compartment was proposed, which usually allows characterizing solubility-limited dissolution or saturable intestinal absorption mechanisms. However, these types of models are purely empirical, whereas mechanistic dissolution/absorption models are more suitable characterizing these processes. In addition, the use of structurally more complex mechanistic models allows reducing the number of covariates on the absorption parameters, which lack physiological meaning (dose in F). On the other hand, it could reduce the large inter-individual variability on ka (95%). The Applicant acknowledged the relevance of non-linear absorption mechanisms and solubility-limited mechanisms involved in the absorption process of danicopan, especially at higher dose levels. However, the Applicant refused to explore the statistical significance of those mechanisms based on the rationale that those dose levels would not be clinically relevant (supratherapeutic). We regret the decision, but this decision requires restricting the use and application of the model for the proposed dose level and dosage regimen. Model-based predictions in higher dose levels or more frequent dose administrations that lead to higher exposure range could not be supported from a regulatory perspective. Extrapolation exercises to other sub-groups of populations would need to be further justified with additional evidence on the similarity of PK processes and disease status.

The food effect is included on F (fasted and high-fat meal), D1 (fasted) and Ka (fasted). Results show a 25% difference in F between fasted and high-fat meals. Ka is increased by 7.15 units in fasted conditions, but the food-effect study suggested an increased exposure when high-fat meal conditions were administered. On the other hand, an 11% higher D1 is estimated in fasted conditions. In this regard, a dose-dependent food effect was identified when evaluating the different impact on exposure PK endpoints between the 200 and 800 mg dose levels.

The differences in food effect are expected between the dedicated food effect study and the population PK model. A similar trend in the impact of fed status was acknowledged with a little impact on the PK exposure metrics (34% lower Ctrough, 15% lower AUC and 9% lower $C_{max}$). However, the results from the food effect study (ACH471-006) do suggest a greater impact on the exposure of danicopan in fed conditions (49% higher for AUClast, 44% higher for AUC0-inf and 102% higher for $C_{max}$). See also SmPC sections 4.2 and 5.2.

In the population pharmacokinetic (PK) analysis in patients with PNH who have clinically significant EVH, the $t_{½}$ has an estimated mean value of 7.91 hours.

Model evaluation through GOF plots suggest a slight over-prediction in the low range of PK concentrations. The visual inspection of prediction-corrected VPC stratified by study is challenging, since no clear evaluation could be performed around the $C_{max}$ region and initial sampling times. In addition, the y-scale is too limited in several pcVPC for representing the prediction interval of the lowest percentile. Analysing the pcVPC of the Phase 3 study, a slight under-prediction of $C_{max}$ is observed for the 50th percentile, which could bias the exposure-safety and exposure-QTc analyses. The Applicant provided additional pcVPC using semi-log scale and normal scale. pcVPC plots by study during the absorption phase for the final PK model with 95% prediction intervals of the 5th, 50th, and 95th percentiles were constructed. pcVPC of study ALXN2040-PNH-301 (PNH patients) showed under-estimation of the inter-individual random effects on the median and 95th percentile. The numerical predictive check over the exposure metrics ($C_{max}$, AUC and Ctrough) has been provided stratified by study design conditions (multiple dose and single dose). Overall, the population PK model tends to under-predict the exposure of danicopan. Although the under-prediction is of minor relevance for AUC and Ctrough, the under-prediction on $C_{max}$ ranges from 5-35% compared to the observed median. This

is of special relevance in case the population PK model is used for predicting changes on $C_{max}$ due to formulation changes or other processes where $C_{max}$ becomes the critical exposure endpoints. The model misspecification on $C_{max}$ is not clinically relevant for the efficacy/safety relationship.

The Applicant evaluated several exposure metrics ($C_{max}$,ss, Ctrough,ss and AUC24h,ss) simultaneously and in a more informative analysis (forest-plot). Results showed a significant increase in exposure ($C_{max}$ss, Ctroughss and AUCss) in patients with severe renal impairment (56%, 35% and 72.5 % respectively) compared to subjects with normal renal function. The final proposed dosing regimens in patients with severe renal impairment (100 to 150 tid) would provide more similar exposure to the reference dosing regimens (150 to 200 tid). The dose scalation to 150 tid would provide a 30% higher AUC compared to the reference regimen of 200 tid. Due to the absence of commercial doses between 100 and 150 mg, the proposal is considered appropriate despite the slight increase in exposure in patients with severe renal failure. Therefore, close monitoring of the safety events is required once they receive 150 mg tid (See clinical safety discussion).

Special populations

- Impaired renal function

A comparison between healthy subjects with normal renal function and severe renal impairment subjects was conducted in Study ACH471-009 following a single dose of 200 mg (2 x 100 mg tablets) of Danicopan under fed conditions. Results showed a significant increase in exposure (AUC0-∞ and AUC0-t) in patients with severe renal impairment (52% and 48% respectively) compared to subjects with normal renal function. The changes in exposure seem to be related to the decrease in CL/F and CLR in patients with severe renal impairment (34% and 51% respectively), which is expected. Taking into account that the mass balance study (ACH471-005) showed that renal excretion contributed by 24% in the excretion of Danicopan, the reduction of CL/R seems to be the main reason for the increased systemic exposure of Danicopan in patients with severe renal impairment. The impact on exposure in patients with severe renal impairment vs. patients with normal renal function is evident, according to the results of the forest plot analysis. Although there is a certain overlap, logically due to the high interindividual variability, the trend of greater exposure is evident in severe RI. Although the PK/PD ratio does not suggest relevant changes in terms of safety, the experimental evidence (n=12) and the PK/PD characterisation in patients with high exposure levels is insufficient to definitively rule out that a higher exposure in patients with severe RI does not translate into a higher incidence of side effects. The impact of mild and moderate renal impairment in the exposure of danicopan has been evaluated graphically using the post-hoc exposure values across the different sub-groups of renal impairment. Overall, the boxplots suggest no relevant differences in the exposure of patients from Study ALXN2040-PNH-301 over the different exposure metrics evaluated (AUC24,ss, Ctrough,ss, $C_{max}$,ss) for patients with mild renal impairment. Based on the forest plot analysis, clinically relevant changes (26%) are expected in Ctrough,ss in patients with moderate renal impairment. Despite the higher Ctrough,ss levels with the proposed dosing regimen, no relevant changes are expected in $C_{max}$,ss or AUC24h,ss. Furthermore, based on the flat exposure-response relationship, those changes are not expected to be clinically meaningful. Therefore, the proposed dosing regimen is considered acceptable for patients with moderate RI (see SmPC sections 4.2 and 5.2

- Impaired hepatic function

A comparison between healthy subjects with normal hepatic function and subjects with moderate hepatic impairment was conducted in Study ACH471-012 following a single dose of 200 mg (2 x 100 mg tablets) of Danicopan under fed conditions. Results showed non-significant changes in exposure (AUC0-∞ and AUC0-t) in patients with moderate hepatic impairment (8% decrease of both parameter) compared to subjects with normal hepatic function. However, a significant decrease in $C_{max}$ (27%) was observed in patients with moderate hepatic impairment.

According to previous studies, Danicopan is extensively metabolised mainly by hydrolysis with minimal CYP mediated pathways. Therefore, it was expected that mild/moderate hepatic impairment would not have an impact on Danicopan exposure.

In Study ACH471-012 a single dose of 200 mg danicopan was tested in patients with normal and moderately-impaired hepatic functions. A significant decrease in $C_{max}$ at patients with moderate hepatic impairment was explained by an impaired biliar flux and consequent reduced solubilisation of the drug since CYP450-mediated enzymatic pathways have negligible role in metabolism of danicopan based on ADME studies. (see SmPC sections 4.2 and 5.2). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

- Gender

Figure 5 and Table 14 aim to represent the impact of covariates on Danicopan steady-state exposure metrics. It is acknowledged that the Applicant evaluated several exposure metrics ($C_{max}$,ss, Ctroug,ss and AUC24h,ss) simultaneously. However, the analysis represents a stochastic simulation incorporating inter-individual random effects. A more informative analysis (forest-plot) should be conducted to fully understand the contribution of each covariate on danicopan exposure. This analysis should be conducted with the final population PK model, as highlighted in the pharmacokinetics in the target population section. In this sense, these results should be considered as provisional.

On the other hand, a graphical comparison using the post-hoc steady state exposure levels between females and males from Study ALXN2040-PNH-301 has been provided. The results clearly suggest a higher exposure in females compared to males with the proposed dosing regimen of 150 mg TID. A numerical comparison using the post-hoc exposure levels was provided. Based on the evidence, 1.31- to 1.48-fold higher than that in male participants for the median or typical patient, in terms of $C_{max}$,ss, Ctrough,ss, and AUC24h,ss was predicted. No relevant differences in the incidence of safety events and efficacy profile was observed after danicopan administration between males and females.

- Race

The final model of danicopan did not identified race as a covariate. Boxplots of post hoc steady state exposures (Ctrough, $C_{max}$, AUC24h) from the phase 3 study ALXN2040-PNH-301 did not show significant differences between populations. Race did not seems to influence the PK of danicopan.

- Weight

Figure 5 and Table 14 aim to represent the impact of covariates on Danicopan steady-state exposure metrics. It is acknowledged that the Applicant evaluated several exposure metrics ($C_{max}$,ss, Ctroug,ss and AUC24h,ss) simultaneously. However, the analysis represents a stochastic simulation incorporating inter-individual random effects.

An additional analysis has been provided evaluating graphically the post-hoc exposure levels of danicopan across different sub-groups of body weight (44-<60, 60-<100, 100-150). The estimated exposure levels at steady state suggest clearly higher exposure in patients with body weight less than 60 kg vs patients of >60 kg. A numerical comparison was provided in order to understand the expected change in exposure in patients. Differences are predicted across the different body weight sub-groups across the dosing regimens tested (150 and 200 tid). A 30% higher exposure is predicted in patients with body weight between 44 to 60 compared to the reference group (>60 to 100 kg). In this regard, higher exposure levels are expected as long as body weight reaches the lower limit (44 kg). As previously stated, based on the large inter-individual variability, it seems very likely that larger differences in exposure could be expected when danicopan is administered in a larger population with body weight <60 kg. The stratified analysis of safety events across the different body weight groups, showing a similar incidence across the different TEAE, which limits the interpretation of the relationship

between exposure and body weight, the trend of greater exposure to lower body weight is evident. Although the E-R relationship is flat, a higher incidence of breakthrough haemolysis, neutropenia and thrombocytopenia is observed compared to the group between 60 and 100 kg. Since the results are based on a small N (25), patients weighing less than 60 kg should be monitored for adverse events during treatment with danicopan.

- Elderly

Part 2 of Study ACH471-016 was performed in a cohort (N=7) of healthy elderly participants to compare PK data from elderly participants to PK data from young participants in Part 1. However, different fed conditions were used in both populations that hampers the assessment of age on danicopan PK.

Based on the populations PK modelling, age was not identified as a significant covariate.

DDI

Study ACH471-010

Danicopan was shown *in vitro* to be an inhibitor of CYP3A, P-gp and both MRP2 and OATP1B1.

The three-part Study ACH471-010 assessed the effect of danicopan on the PK of midazolam (on the activity of CYP3A), fexofenadine (on the activity of P-gp) and the PK of both MPA (on the activity of UGTs and CYP2C8) and MPAG (on the activity of P-gp and MRP2).

Following co-administration of oral danicopan and midazolam, based on GMR, midazolam showed an increase in $C_{max}$ and AUC0-t (22% and 23% respectively) compared to the single administration. The coadministration did not affect the value of t1/2 of midazolam. However, CL was decrease when danicopan was coadministered with midazolam. The results suggest that danicopan is a weak inhibitor of CYP3A4.

Following co-administration of oral danicopan and fexofenadine, based on GMR, fexofenadine showed an increase in $C_{max}$ and AUC0-t (59.53% and 42.28% respectively) compared to fexofenadine alone. The coadministration significantly increased t1/2 and decreased CL. Fexofenadine is also a substrate of OATP transporter. The effect of danicopan on OTP transporter is unknown. The results suggest that danicopan is a mild inhibitor of P-gp. The SmPC has been updated in order to incorporate the information regarding the effect of Danicopan on P-pg substrates, which is endorsed.

Comparable exposure of MPA and MPAG (MMF metabolites) was observed following single administration of MMF or coadministration with danicopan. The Results suggest that danicopan does not inhibit the activity of UGT.

In Study ACH471-010, danicopan was observed as a weak inhibitor of CYP3A4, P-gp, but appeared no inhibitory activity on UGT.

Study ACH471-014

The three-part Study ACH471-014 assessed the two way interaction between danicopan and cyclosporine, tacrolimus, antacids, and omeprazole in healthy adult participants.

Following co-administration of oral danicopan and cyclosporine, based on GMR, cyclosporine showed an increase in AUC0-t (23%) and no change in $C_{max}$ (2.72%) compared to the single administration. The t1/2 value of cyclosporine slightly increased and CL was decreased when danicopan was coadministered with cyclosporine. On the other hand, danicopan also showed a slight increase in AUC0-8 (21.2%) and $C_{max}$ (14.42%) when administered in combination with cyclosporine.

Following co-administration of oral danicopan and tacrolimus, based on GMR, tacrolimus showed an increase in AUC0-t (54.64%) and slight increase in $C_{max}$ (13%) compared to tacrolimus alone. The coadministration did not affect the t1/2 and decreased CL. On the other hand, danicopan also showed a slight increase in AUC0-8 (20.32%) and $C_{max}$ (18.65%) when was administered in combination with cyclosporine.

Following co-administration of oral danicopan and antacids (calcium carbonate and aluminium/magnesium hydroxide/simethicone) based on GMR, AUC0-8 and $C_{max}$ of danicopan had values ranging (22-31% higher) compared to exposure of danicopan alone. The effect on the exposure does not seem to be clinically relevant.

The combination with omeprazole increased $C_{max}$ 21% but it did not affect AUC0-8. Based on the results, danicopan seem to be a weak inhibitor of CYP2C19. On the other hand, omeprazole exposure was comparable following the administration of the combination and omeprazole administered alone (AUC0-24h and $C_{max}$ were approximately 17% and 24% higher respectively).

In Study ACH471-014 danicopan was proved to be a weak, clinically insignificant inhibitor of CYP3A4. The reduced $C_{max}$ at patients with moderate hepatic impairment was explained by a reduced biliary function.

Study ACH471-017

The three-part Study ACH471-014 assessed the two way interaction between danicopan and warfarin, bupropion, and ethinyl estradiol and norethindrone (EE and NET).

Regarding the coadministration of warfarin and danicopan, the exposure of R-warfarin was similar compared to administration of warfarin alone. The exposure of S-warfarin was slightly higher when was administered in combination, based on GMR values, differences of 4.52% in $C_{max}$ and 13.54% in AUC0-t. These results suggest that danicopan is not an inhibitor or inducer of CYP2C9 or CYP1A2. On the other hand, danicopan exposure was lower when administered in combination with values of $C_{max}$ and AUC0-8 19% and 17% lower respectively. The differences in exposure were not clinically significant.

Following co-administration of oral danicopan and bupropion, based on GMR, bupropion showed a slight increase in AUC0-t (11.4%) and in $C_{max}$ (5.13%) compared to bupropion alone. The results suggest that danicopan is not a significant inhibitor of CYP2B6. On the other hand, danicopan exposure was lower when administered in combination with values of $C_{max}$ and AUC0-8 14% and 12% lower respectively. The differences in exposure were not clinically significant.

Following co-administration of oral danicopan and EE and NET, based on GMR, EE exposure showed an increase in AUC0-t (29.5%) and a slight increase in $C_{max}$ (7%), NET exposure also showed an increase in AUC0-t (14.32%) and $C_{max}$ (3.4%). On the other hand, danicopan exposure decreased slightly following the coadministration with EE/NET compared to administration alone with values of $C_{max}$ and AUC0-8 of 14% and 17% respectively. These results suggest that the interaction was not clinically significant.

**Pharmacodynamics and Pharmacokinetics-Pharmacodynamics (PK/PD)**

In studies conducted for the assessment of danicopan's pharmacodynamic features in healthy participants and patients with PNH, the primary endpoints were the measurement of biomarkers as AP activity, serum Bb concentrations, total FD and C3 concentrations and CP activity. Measurement was performed by semi-quantitative, ex vivo AP activity assays (APW and APH).

The studies demonstrated that danicopan inhibits a significant, dose-dependent ex and *in vivo* inhibition of the AP of the complement system as can be observed in serum AP activity and plasma Bb

concentrations, moreover studies in patients with PNH showed that danicopan reduces the C3 fragment deposition on circulating red blood cells.

In PD part of Study ACH471-001, participants received higher doses of danicopan (600-1200-2400 mg) exhibited considerably high alternative pathway (AP) activity and plasma complement Bb concentration after 24 hours of drug administration.

The measurement of the abovementioned biomarkers are useful and attractive methods for studying the entire spectrum of the complement system, however other sensitive biomarkers (eg.: properdin, C3b) of alternative pathway (AP) activity could have been measured to demonstrate danicopan's effect in the PD part of studies (Study ACH471-001, Study ACH471-002).

Danicopan produced inhibition of AP and Bb in patients with PNH (Study ACH471-100) with mean values at day 84 of 14.43% AP and 0.467 µg Bb and changes from baseline to day 84 of -52.26 and -1.52 respectively. However, minimal effect was observed on total FD concentrations and CP activity with mean values at day 84 of 2816.4 ng/mL FD and 119 CAE units CP and changes from baseline -85.5 and -136.5 respectively. These results are in agreement of the proposed mechanism of action of danicopan.

The phase 3 study (ALXN2040-PNH-301) assessed the PD of danicopan as an add-on therapy to a C5 inhibitor (ravulizumab or eculizumab) in PNH patients with evident EVH. Patients who continue to experience anaemia with or without transfusions were randomised to danicopan tid of placebo tid in addition to their eculizumab or ravulizumab therapy. Participants treated with danicopan had mean trough concentrations above 200 mg during the 12 weeks dosing period and experience complete AP activity inhibition (mean values <10%) following the first dose until the end of treatment.

APW PK/PD model

The Applicant has evaluated the relationship between APW and danicopan exposure through a longitudinal PK/PD model, which is appreciated. However, most of the data has been collected in healthy volunteers (n=110), while there is only information in 10 PNH patients to elaborate the PK/PD model. This represents a relevant limitation for establishing dosing recommendations in the target population (PNH patients).

The modeling strategy and data management are endorsed, especially for BLQ observations, which evaluated alternative BLQ methods showing no relevant discrepancies among them. The log-linear PK/PD model adequately characterised the relationship between danicopan and APW. The covariate analysis shows a reduction in baseline in PNH patients compared to healthy volunteers (32%). On the other hand, the baseline APW on KK was identified as a significant covariate, such that high baseline APW values show a lower reduction capacity (KK) of APW for the same concentration of danicopan. Diagnostic plots show that the current PKPD model under-predicts the effect of Danicopan (APW activity) on PNH patients. Further refinement is necessary to consider the model suitable for prospective dosing regimen evaluation.

APH PK/PD model

A PK/PD model has been proposed to evaluate the relationship between danicopan and APH in 69 subjects with PNH (Study ALXN2040-PNH-301). The modeling strategy and data management are endorsed, especially for BLQ observations. Regarding the relationship between APH and Hgb/LDH, the lack of a wider range of exposure led to a flat and non-significant exposure-response relationship that would help to justify the proposed and alternative dosing regimens.

An $E_{max}$ model has been proposed to explain the relationship between danicopan exposure and APH longitudinal levels. Then, a covariate analysis identified weight and East Asian on baseline APH. The overall model evaluation through GOF and VPC confirm the adequacy of the model to characterise the observed data, although the residual error and inter-individual variability on IC50 are very large (67% and 229%, respectively).

Diagnostic plots show that the current PKPD model under-predicts the effect of Danicopan (APH activity) on PNH patients. Further refinement is necessary to consider the model suitable for prospective dosing regimen evaluation.

The Applicant clarified that the current PK/PD model of APH is not aimed to be used for exploring alternative dosing regimens since several limitations were found and could bias the results. Therefore, no dose recommendations are based on the PK/PD of APH and further model evaluations using the current PK/PD framework should not be considered.

QTc prolongation

The evaluation of the relationship between danicopan concentration and QTc prolongation has been conducted in a Phase 1 study in healthy volunteers receiving different dose levels (400- 800 and 1200 mg). The QTc prolongation has been studied in healthy patients at fasted status receiving supratherapeutic doses of 400 mg, 800 mg and 1200mg of danicopan. The geometric mean $C_{max}$ of danicopan for the 3 doses were 535, 870 and 1027 ng/ml respectively. At the highest concentration investigated (1200mg), $C_{max}$ was 1.24- (fed) to 2.4-fold (fasting) greater than the $C_{max}$ value at the maximum therapeutic dose of 200 mg with a high-fat/high-calorie meal (826 ng/mL).

A linear model was developed using baseline in QTcF vs danicopan predicted concentrations. The model evaluation suggest the adequacy of the linear model to characterise such relationship, although Figure 22 indicates an under-prediction of high (>10 ms) and an over-prediction of low (<-10 ms) dQTcF values, which could influence the model predicted dQTcF values at the predicted plasma concentrations (Figure 23). The expected change in QTcF from baseline is less than 4 ms in the upper limit of the 90% confidence interval of the $C_{max}$ of the highest dose (1200 mg), showing the likely lack of clinically relevant changes in QTc after danicopan administration.

Exposure-Response

- Exposure-efficacy

The exposure-efficacy evaluation has been conducted over several efficacy endpoints (relative change in Hgb to baseline, proportion of patients with Hgb increase of $\geq$ 2 g/dL, and transfusion avoidance) measured at Week 12 vs PK exposure endpoints (AUC24,ss, Ctrough,ss). The statistical assessment is purely based on simple linear regression models or visual inspection of boxplot of danicopan grouped by each category. These analyses serve to indicate trends and confirm expected results: the greater the exposure of danicopan, (i) the greater change in Hgb from baseline and (ii) the lower proportion of patients with Hgb increase of $\geq$ 2 g/dL.

However, they do not allow predicting the time course of Hgb or predicting the probability of transfusion or the proportion of patients with Hgb increase of $\geq$ 2 g/dL over time linking danicopan exposure, since they only assess at one point in time (Week 12). Thus, they are not informative for evaluating dosing strategies or the impact of disease-related or patient/population-related covariates in future clinical studies.

- Exposure-safety

The exposure-safety evaluation has been conducted over several safety endpoints. The descriptive analysis aims to link the incidence of safety adverse events vs placebo and treated subjects across

different quartiles of danicopan exposure. For that aim, $C_{max}$,ss and AUC24,ss have been considered as the exposure endpoints. The evaluation is limited to the exposure at Week 12, which represents an important limitation to understand the evolution of security over time. The results indicate a positive trend of increased arthralgia, diarrhoea, headache, and hypertension at high danicopan exposure ranges.

The incidences do not exceed 20% for the dosing regimens evaluated in the study, except for hypertension (25% for Q4). These are manageable adverse effects, easy to diagnose and reversible.

The impact of higher exposure ($C_{max}$,ss and AUC24h,ss) after concomitant administration of normal and high-fat meal in patients receiving danicopan has been evaluated based on the incidence of adverse events. No clear relationship was established between higher exposure and a higher incidence of adverse events. Therefore, no need for dose adjustment has been demonstrated when danicopan is administered with food.

## 2.6.4. Conclusions on clinical pharmacology

Pharmacokinetics of danicopan have been characterised through non-compartmental and compartmental analyses, evaluating the main aspects in terms of clinical pharmacology. The Applicant has evaluated the relationship between AP activity and danicopan exposure through two different longitudinal PK/PD model based on APW and APH assays. The modelling strategy and evaluation is endorsed. Clinical pharmacology aspects are adequately described and relevant information has been included in the SmPC sections 4.2 and 5.2.

## 2.6.5. Clinical efficacy

### *2.6.5.1. Dose response study(ies)*

The selected dose for danicopan (i.e. 150 mg) was based on the safety data of all patients treated with danicopan in studies ACH471-101, ACH471-100, ACH471-103, ACH471-201, ACH471-204, and ACH471-205, along with the efficacy data observed in study ACH471-101 (danicopan + C5 inhibitor) and PK/PD modeling and simulation.

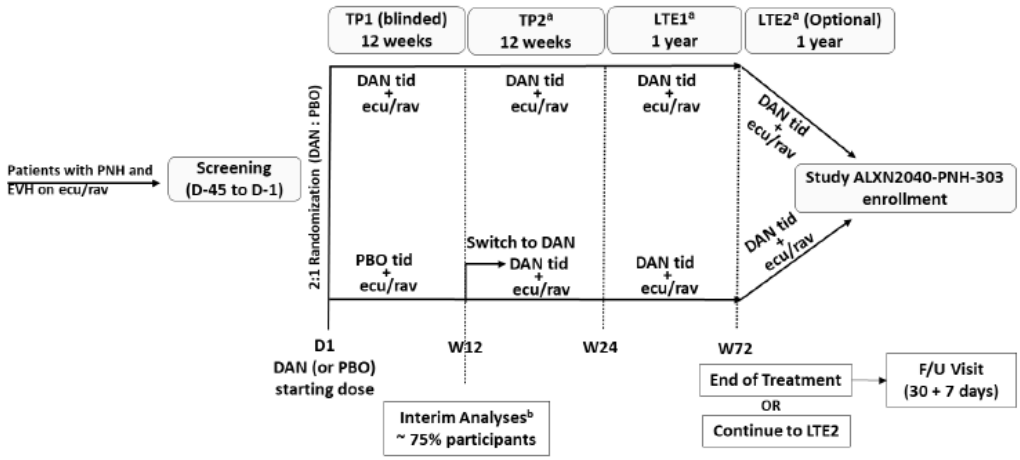
In the Phase 2 study ACH471-101 danicopan doses ranging from 100 to 200 mg tid showed to be clinically effective and generally well tolerated in patients with PNH on a C5 inhibitor. In this study, 150 mg tid was a reasonable effective starting dose in a subset of patients, with upward titration based on clinical response to 200 mg tid.

### *2.6.5.2. Main study(ies)*

#### ***Study ALXN2040-PNH-301: A Phase 3 Study of danicopan (ALXN2040) as add-on therapy to a C5 Inhibitor (eculizumab or ravulizumab) in patients with paroxysmal nocturnal haemoglobinuria who have clinically evident extravascular haemolysis (EVH)***

This is an ongoing multiple-region, randomised, double-blind, placebo-controlled, multiple-dose, Phase 3 study in participants with PNH who have clinically significant EVH while on treatment with background eculizumab or ravulizumab.

The study consists of 2 treatment periods and a Long-term Extension (LTE) Period, as described below.




Note: Dose escalations to a maximum of danicopan 200 mg tid at specified timepoints W6, W12, and W18 during TP1 and TP2 and at any time during the LTE. See dose escalation guidelines in Appendix 16.1.1 Protocol and Protocol Amendments Section 6.6.

[a] After TP1, all placebo participants were switched to danicopan and remained on danicopan throughout the study. TP1 treatment allocation remained blinded until interim database lock.

[b] As of the interim analysis cutoff date (28 Jun 2022), 73 participants were randomized, 61 participants completed TP1, and 2 participants discontinued TP1.

Abbreviations: D = day; DAN = danicopan; ecu = eculizumab; EVH = extravascular hemolysis; F/U = follow up; LTE1 = Long-term Extension Year 1; LTE2 = Long-term Extension Year 2; PBO = placebo; PNH = paroxysmal nocturnal hemoglobinuria; rav = ravulizumab; tid = 3 times daily; TP1 = Treatment period 1; TP2 = Treatment period 2; W = week

**Figure 29: ALXN2040-PNH-301 Study Schematic**

***Methods***

- **Study Participants**

Main inclusion criteria

1. Diagnosis of PNH.
2. Clinically evident extravascular haemolysis (EVH) defined by:
    - Anaemia (**Hgb ≤ 9.5 g/dL**) with **absolute reticulocyte count ≥ 120 × $10^9$/L**.
3. Receiving an approved **C5 inhibitor for at least 6 months** prior to Day 1 in this study at an approved dose (or higher) and with no change in the prescribed dose or interval for at least 24 weeks preceding Day 1. For those patients who recently switched from eculizumab to ravulizumab, they must have received at least the loading dose and 3 maintenance doses (minimum of 24 weeks) of ravulizumab preceding Day 1. Infusions outside the prescribed interval due to a logistical reasons/patient convenience are not considered a change in the prescribed interval and should be discussed with the Medical Monitor prior to randomisation.
4. Platelet count ≥ 30,000/$\mu$L without the need for platelet transfusions.
5. Absolute neutrophil counts (ANC) ≥ 500/$\mu$L.
6. Documentation of vaccination for *N. meningitidis*: All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

7. Age 18 years or older (or greater than or equal to minimum adult age in accordance with local legal requirements).
8. Patients who are on iron, folic acid, and vitamin B12 supplementation are eligible for the study if on a stable dose for at least 30 days prior to Day 1.

Main exclusion criteria

1. History of a major organ transplant (e.g., heart, lung, kidney, liver) or HSCT.
2. Known aplastic anaemia or other bone marrow failure that requires HSCT or other therapies including anti-thymocyte globulin and/or immunosuppressants, unless the dosage regimen of immunosuppressant has been stable for at least 12 weeks before Day 1 and patient is expected to remain on stable doses through Week 24.
3. Received another investigational agent other than C5 inhibitors (eculizumab or ravulizumab) within 30 days or 5 half-lives of the investigational agent prior to study entry, whichever is greater.
4. Known or suspected complement deficiency.
5. Known underlying bleeding disorders (eg, coagulation factor deficiencies, idiopathic thrombocytopenic purpura, Von Willebrand disease, etc.) or any conditions leading to anaemia that are not primarily due to PNH.
6. Active bacterial or viral infection, a body temperature >38°C on two consecutive daily measures, evidence of other infection, or history of any febrile illness within 14 days prior to first study drug administration.
7. History or presence of any clinically relevant co-morbidities that would make the patient inappropriate for the study (eg, is likely to result in deterioration of the patient's condition, affect the patient's safety during the study, or confound the results of the study).
8. Laboratory abnormalities at screening, including:
    - ALT > 2 × ULN (> 3 × ULN in the case of patients with documented liver iron overload defined by serum ferritin values ≥ 500 ng/mL). The inclusion of patients with documented iron overload and ALT > 2 × ULN will be done in a case by case basis, with prior discussion with the Medical Monitor.
    - Direct bilirubin > 2 × ULN, with the exception of:
        - patients who, in the opinion of investigator, have direct bilirubin > 2 × ULN due to EVH and/or
        - patients with documented Gilbert's syndrome (if Gilbert's syndrome is suspected, the patient will be tested for this condition at screening).
9. Any other clinically significant laboratory abnormality as judged by the Investigator that, in the opinion of the Principal Investigator, would make the patient inappropriate for the study or put the patient at undue risk.
10. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration.
11. Current evidence of biliary cholestasis.
12. Evidence of hepatitis B (positive hepatitis surface antigen [HBsAg] or positive core antibody [anti-HBc] with negative surface antibody [anti-HBs]) or hepatitis C viral infection (HCV antibody

positive), except for patients with documented successful treatment and documented sustained virologic response (SVR) at Screening

13. Evidence of human immunodeficiency virus (HIV antibody positive) infection at Screening
14. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 and/or are on dialysis.
15. Hypersensitivity to the investigational drug (danicopan) or any of its excipients.

- **Treatments**

The planned starting dose of danicopan was 150 mg tid. Doses of study drug (danicopan or placebo) could be escalated to a maximum of 200 mg tid, based on safety and clinical effect, at specified time points during the initial treatment period and during the LTE Period. Any dose escalation was done after a minimum of 4 weeks at each dose level.

All participants were to be treated with danicopan in combination with a C5i therapy (i.e., eculizumab or ravulizumab) at stable doses. In countries where ravulizumab is not approved, local amendments were issued to provide ravulizumab as an IMP.

Participants could not switch between eculizumab and ravulizumab therapy during the first 24 weeks but may do so during the LTE Period. The only switch allowed was from eculizumab to ravulizumab.

Participants discontinuing from the study undergo tapering of study intervention over 6 days (Taper Visit 1 and 2), and a Follow-up Visit approximately 30 days after the last dose of study intervention during the Tapering Period. Participants continue to receive ravulizumab or eculizumab therapy at the same dose and interval that they were receiving during the Taper and Follow-up Visits.

- **Objectives and Outcomes/endpoints**

**Table 33: Study ALXN2040-PNH-301 efficacy objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor at 12 weeks | • Change in hemoglobin (Hgb) relative to Baseline after 12 weeks of treatment with danicopan compared to placebo |
| **Secondary** | |
| **Key secondary** | |
| • To evaluate the efficacy of danicopan on Hgb improvement in absence of transfusion as compared to placebo as add-on therapy to a C5 inhibitor at 12 weeks | • Proportion of patients with Hgb increase of ≥ 2 g/dL (≥ 20 g/L) at Week 12 in the absence of transfusion |
| • To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on transfusion avoidance (TA) at 12 weeks | • Proportion of patients with TA, defined as patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines through Week 12 |
| • To evaluate the effect of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores for 12 weeks of treatment | • Change from Baseline in FACIT-Fatigue scores at Week 12 |
| • To evaluate the effect of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on absolute reticulocyte count | • Change from Baseline in absolute reticulocyte count at Week 12 |
| **Other secondary** | |
| • To evaluate the efficacy of danicopan as add-on therapy to a C5 inhibitor on transfusion requirements at 24 weeks for those patients receiving 24 weeks of danicopan | • Change in the number of red blood cell (RBC) units transfused and transfusion instances during the 24 weeks of treatment with danicopan compared to the 24 weeks prior to initiation of treatment with danicopan<br>• Percentage of patients who have TA through 24 weeks of treatment |
| • To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on transfusion requirements at 12 weeks | • Change in the number of RBC units transfused and transfusion instances during the 12 weeks of treatment with danicopan compared to the 12 weeks while receiving placebo |
| • To evaluate the effect of danicopan as add-on therapy to a C5 inhibitor on FACIT-Fatigue scores for 24 weeks of treatment | • Change from Baseline in FACIT-Fatigue scores at Week 24 in all patients |

| Objectives | Endpoints |
|---|---|
| • To assess the efficacy of danicopan as add-on therapy to a C5 inhibitor on Hgb stabilization | • Percentage of patients with Hgb stabilization during the last 12 weeks of treatment in patients receiving 24 weeks of danicopan |
| • To evaluate the efficacy of danicopan on Hgb improvement in absence of transfusion as add-on therapy to a C5 inhibitor at 24 weeks | • Proportion of patients with Hgb increase of ≥ 2 g/dL (≥ 20 g/L) at Week 24 in the absence of transfusion |
| • To assess additional laboratory markers relevant in PNH patients | • Change from Baseline of danicopan treated patients compared to placebo in total and direct bilirubin at 12 weeks<br>• Changes in PNH RBC clone size and C3 fragment deposition on PNH RBCs at 12 weeks of treatment with danicopan compared to placebo<br>• Changes in lactate dehydrogenase (LDH) at 12 weeks<br>• Percentage of patients with Hgb normalization at 12 weeks and 24 weeks |
| **Exploratory[a]** | |
| • To assess patient-reported outcomes (PRO) and other health-related quality of life (QoL) measures during 24 weeks of treatment | • Change from Baseline relative to placebo in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30) at Week 12<br>• Change from Baseline in EORTC-QLQ-C30 scale at Week 24 |

[a] Other prespecified exploratory endpoints not described in this Summary of Clinical Efficacy are included in ALXN2040-PNH-301 Interim CSR.

Abbreviations: C3 = complement component 3; C5 = complement component 5; PNH = paroxysmal nocturnal hemoglobinuria

It was recommended to administer pRBC transfusion when a subject has a:

1. Hemoglobin value of less than 7 g/dL regardless of presence of clinical signs or symptoms, or
2. Hemoglobin value of less than 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion.

- **Sample size**

A total of approximately 84 patients were planned to be enrolled into this study. It was anticipated that approximately 10% of patients would discontinue prior to the analysis of the primary endpoint. For the primary endpoint of change from baseline to Week 12 in Hgb level, the statistical power using 2-sample t-test is 99% to detect the difference in mean change from Baseline of 2 g/dL (alternative hypothesis), assuming the 2-sided statistical significance level of 0.05 and the SD of 1.6 g/dL, which was estimated from results of Study ACH471-101.

For the key secondary endpoint of patients with TA, the study has 70% power for significant difference between treatment groups, assuming 90% of patients in the danicopan arm and 64% of patients in the placebo arm will have TA. For the key secondary endpoint of change from baseline to Week 12 in FACIT-Fatigue scores, the study has 91% power with 2-sample t-test to detect 9-point difference between treatment arms in mean change from baseline, which is considered clinically meaningful. The

power calculation is based on the assumption of an SD of 11 for FACIT-Fatigue change, which was observed in Study ALXN1210-PNH-301 in PNH patients. The power is 80% based on the SD assumption of 13, which was observed in Study ACH471-101.

- **Randomisation and Blinding (masking)**

This is a double-blind, placebo-controlled study with 2:1 randomisation. The randomisation scheme was stratified by transfusion history (ie, > 2 or ⩽ 2 transfusions within 6 months of Screening), Hgb (ie, < 8.5 g/dL and ⩾ 8.5 g/dL) at Screening, and Japanese patients (defined as patients enrolled from Japan)/non-Japanese patients.

- **Statistical methods**

Analysis populations

- Intent-to-treat (ITT) population: All randomised patients; data will be analysed by the treatment groups to which patients are randomly assigned, even if the patient does not take the assigned treatment, does not receive the correct treatment, or does not comply with the protocol.
- Per Protocol population: Intent-to-treat (ITT) patients who do not have protocol deviations expected to affect the primary efficacy endpoint (Week 12). Such protocol deviations will be prespecified in the statistical analysis plan prior to database lock.
- Safety population: All patients who take at least one dose of study drug.

Efficacy analyses

The **primary efficacy endpoint**, change in haemoglobin at Week 12 relative to baseline between danicopan and placebo, will be analysed using a mixed model for repeated measures (MMRM) which includes the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline haemoglobin value and the stratification randomisation indicator of transfusion history in the model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary efficacy analysis will be the difference between danicopan and placebo arms at Week 12 and the test will be conducted at a 2-sided 0.05 significance level. The primary efficacy analysis is based on the ITT population.

Secondary efficacy analyses will be conducted on the ITT population. **Key secondary efficacy endpoints** were analysed using a hierarchical fixed sequence test procedure to determine the statistical significance at a two-sided level of 0.05 for each endpoint sequentially.

1. Difference in proportion of patients with Hgb increase of ⩾ 2 g/dL at Week 12 in the absence of transfusions.
2. Difference in proportion of patients with RBC transfusion avoidance between danicopan and placebo groups during the 12 weeks of treatment.
3. Difference in changes from baseline in FACIT-Fatigue scores between danicopan and placebo groups at Week 12.
4. Difference in changes from baseline in absolute reticulocyte counts between danicopan and placebo groups at Week 12.

Interim analysis

According to the protocol, an interim analysis may be conducted at the discretion of the study sponsor (based on enrollment progression) when approximately 75% of patients have been randomly assigned to study treatment and have had the opportunity to complete the 12-week Treatment Period 1 (information fraction = 0.75). The purpose of the interim analysis was to evaluate the study for stopping early for efficacy. If conducted, the primary endpoint of change in Hgb levels at Week 12, as well as the key secondary endpoints were to be evaluated using the alpha-spending methods specified below to control family-wise error rate.

- The evaluation of primary endpoint at interim analysis would be using the gamma family alpha-spending function (Hwang, 1990) with parameter -4. Specifically, the alpha level assigned for the primary endpoint at interim is 2-sided 0.018. Correspondingly, if the interim analysis is conducted, the nominal significance level for the primary endpoint at the final analysis is 2-sided 0.046.
- The evaluation of key secondary endpoints at interim analysis would be using the gamma family alpha-spending function with parameter 1. Specifically, the alpha level assigned for key secondary endpoint at interim is 2-sided 0.042. Correspondingly, if the interim analysis is conducted, the nominal significance level for key secondary endpoints at the final analysis is 2-sided 0.024.

The recommendation of stopping study enrollment and placebo-controlled Treatment Period 1 for efficacy could be made only if, at a minimum, the primary endpoint and the key secondary endpoints of proportion of patients with Hgb increase ≥ 2g/dL in the absence of transfusion and proportion of patients with transfusion avoidance through the 12week Treatment Period 1 met the prespecified significance level.

***Results***

- **Participant flow**

As of the interim data cut-off date (28 June 2022), 105 participants have signed the ICF, of which 23 were screen failures, 9 were in Screening, and 73 were randomised in a 2:1 ratio to danicopan (n = 49) and placebo (n = 24), of which 63 patients are included in the interim efficacy analysis set. Twelve participants failed initial Screening, were rescreened, and subsequently enrolled in the study.

During the procedure, results of two additional interim analyses (IA) were provided. As of IA3 (31 Mar 2023) 86 participants were randomised in a 2:1 ratio to danicopan (N = 57) or placebo (N = 29). A total of 82 participants completed TP1 (55 in danicopan and 27 in placebo groups) and entered TP2. During TP1, 4 of 86 randomised participants (2 randomised to danicopan and 2 randomised to placebo) discontinued treatment, 3 of whom (2 danicopan and 1 placebo) discontinued treatment due to AEs.

Of the **82 patients** who entered TP2, 80 participants completed TP2 and entered the LTE Year 1. In TP2, 2 participants (1 in the DAN/DAN group and 1 in the PBO/DAN group) discontinued treatment due to AEs. As of the data cutoff date, there were no participants ongoing in TP1 or in TP2, and 58 participants were ongoing in the LTE. Thirty two participants have completed Year 1 of the LTE, and 15 participants have completed the entire LTE. A total of 7 participants discontinued treatment during the LTE (6 DAN/DAN and 1 PBO/DAN), of which 1 participant (PBO/DAN) discontinued treatment due to AEs.

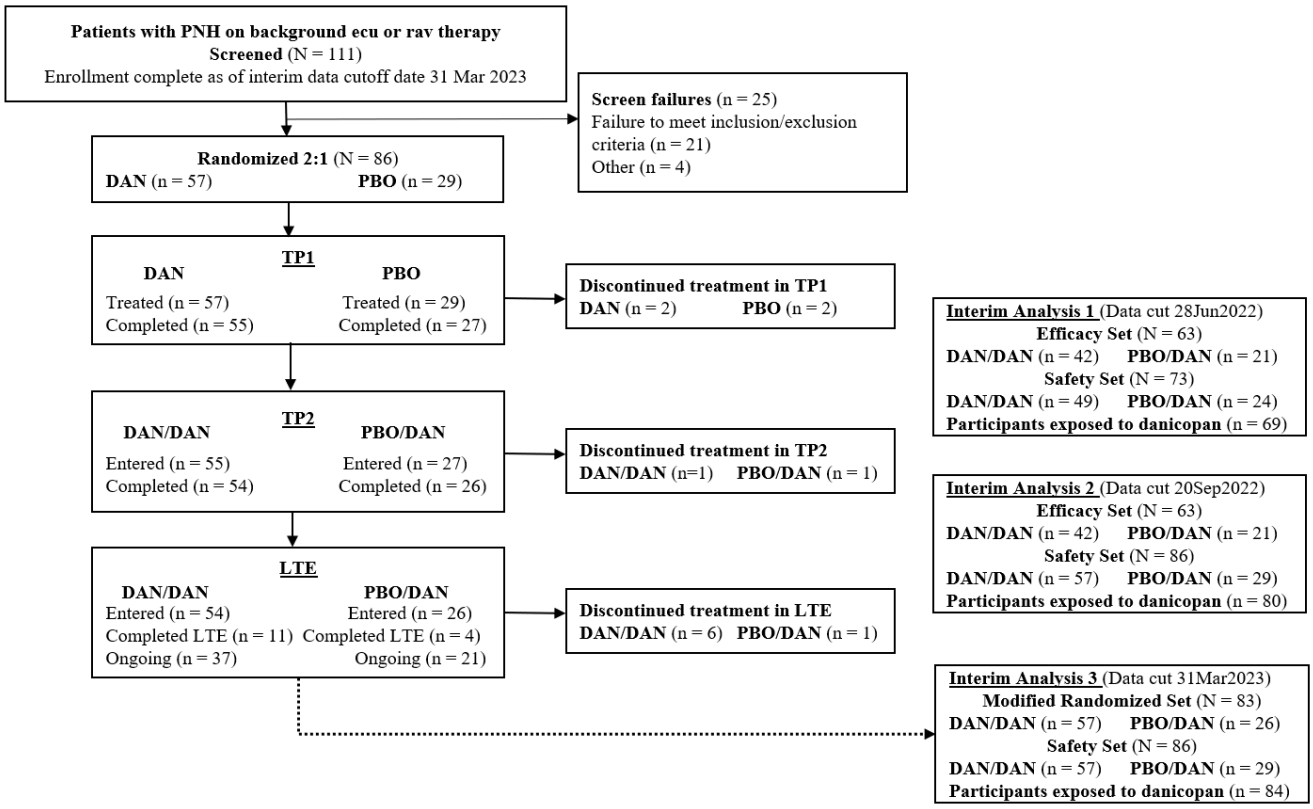



**Figure 30: Participant Disposition (CONSORT diagram)**

**Table 34: Study Disposition – All Randomised Participants**

| Category | Danicopan (N = 57) n (%) | Placebo (N = 29) n (%) | Total (N = 86) n (%) |
|---|---|---|---|
| Randomized | 57 (100) | 29 (100) | 86 (100) |
| Treated (danicopan or placebo)[a] | 57 (100) | 29 (100) | 86 (100) |
| **Treatment Disposition** | | | |
| **Treatment Period 1 (TP1)** | **DAN** | **PBO** | **Total** |
| Ongoing | 0 | 0 | 0 |
| Completed | 55 (96.5) | 27 (93.1) | 82 (95.3) |
| Discontinued treatment | 2 (3.5) | 2 (6.9) | 4 (4.7) |
| Reasons for discontinuation of treatment from TP1 | | | |
| Adverse event | 2 (3.5) | 1 (3.4) | 3 (3.5) |
| Withdrawal by participant | 0 | 1 (3.4) | 1 (1.2) |
| **Treatment Period 2 (TP2)** | **DAN/DAN[b]** | **PBO/DAN[c]** | **Total** |
| Entered TP2 | 55 (96.5) | 27 (93.1) | 82 (95.3) |
| Ongoing | 0 | 0 | 0 |
| Completed | 54 (94.7) | 26 (89.7) | 80 (93.0) |
| Discontinued treatment | 1 (1.8) | 1 (3.4) | 2 (2.3)[d] |
| Reasons for discontinuation of treatment from TP2 | | | |
| Adverse event | 1 (1.8) | 1 (3.4) | 2 (2.3) |
| **Long-Term Extension (LTE)[e]** | **DAN/DAN[b]** | **PBO/DAN[c]** | **Total** |
| Entered LTE | 54 (94.7) | 26 (89.7) | 80 (93.0) |
| Ongoing | 37 (64.9) | 21 (72.4) | 58 (67.4) |
| Completed | 11 (19.3) | 4 (13.8) | 15 (17.4) |
| Completed LTE (Year 1) | 20 (35.1) | 12 (41.4) | 32 (37.2) |
| Discontinued treatment | 6 (10.5) | 1 (3.4) | 7 (8.1) |
| Reasons for discontinuation of treatment from LTE | | | |
| Adverse event | 0 | 1 (3.4) | 1 (1.2) |
| Noncompliance with study intervention | 1 (1.8) | 0 | 1 (1.2) |
| Physician decision | 2 (3.5) | 0 | 2 (2.3) |
| Withdrawal by participant | 3 (5.3) | 0 | 3 (3.5) |

- **Recruitment**

This study is being conducted at 80 centres in 16 countries in Europe, North America, South America, and Asia. First patient was randomised on 06 Jan 2021.

- **Conduct of the study**

The original protocol was dated 18 Nov 2019. The key substantial changes that were implemented across these amendments are detailed in the table below.

**Table 35: Key Substantial Changes across Protocol Amendments**

| Amendment Number, Type (Date) | Change(s) Implemented |
|---|---|
| Amendment 1, Global (17 Apr 2020) | • Major administrative updates made:<br>o Sponsor name change from Achillion Pharmaceuticals, Inc to Alexion Pharmaceuticals Inc., danicopan compound number ACH0144471 to ALXN2040, and study number ACH471-105 to ALXN2040-PNH-301.<br>o All changes resulting from new Sponsor's process and language were added.<br>• Study was changed to a double-blind design, and this was reflected in the schedule of assessments, other sections, and operational aspects.<br>• Patient population was specifically defined as those with extravascular hemolysis (EVH).<br>• Vaccination requirements were clarified.<br>• Study sample size was increased.<br>• Key secondary endpoints and other secondary endpoints were clarified.<br>• Analysis of primary endpoint and secondary endpoints was clarified.<br>• Interim analysis was added.<br>• New sections on DMC and transfusion guidelines before and during the study were added.<br>• Section on individual stopping criteria was deleted. Individual and study stopping requirements were updated in the study stopping criteria section.<br>• PRO and QoL assessments were added; laboratory assessments were updated to include additional assessments.<br>**Updates to inclusion and exclusion criteria**:<br>o Inclusion: The criterion on anaemia was defined further to be linked to clinically evident EVH and transfusion.<br>o Exclusion: Clarity was provided on laboratory abnormalities. |
| Amendment 2, Global (10 Jun 2020)<br><br>Amendment 2.1, Local for multiple countries (10 Jun 2020) | **Global and local amendments:**<br>• Clarified to distinguish between concomitant and background therapies.<br>• Added review of the safety card at various timepoints in the schedule of assessments tables.<br>• Added a new section (Section 6.8) on intervention after the end of the study.<br>• Added information on blind breaking.<br>**Local amendment only (in countries where ravulizumab is not approved)**:<br>• New safety objective and endpoint were added to evaluate immunogenicity in participants receiving ravulizumab as an investigational drug.<br>• Duration of male and female contraception to be observed after the last dose of study intervention was prolonged to reflect requirements for ravulizumab.<br>• Follow-up period was extended to 56 days to reflect requirements for ravulizumab.<br>• Schedule of assessments was updated to reflect the use of ravulizumab as study intervention.<br>• Details on the dosing regimen, and preparation and handling of ravulizumab were provided.<br>• Process of risk management for infections was added for clarification.<br>• Clarification on interventions after end of study was provided.<br>• Information on blind breaking was added.<br>• Added new exclusion criterion on hypersensitivity to the IMP or any of its excipient. |

| | |
|---|---|
| Amendment 3.0, Global (11 Aug 2020)<br><br>Amendment 3.1, Local for multiple countries (20 Aug 2020) | **Global and local amendments:**<br>Text in specific sections to clarify potential risk of hepatic injury and guidance for participant discontinuation was updated.<br>Added language that approved dosages of the background C5 inhibitors are to be used.<br>Added information on switching between different C5 inhibitors.<br>Added text to mitigate the risk of unblinding in relation to certain laboratory tests.<br>Added details on data protection with respect to data security.<br>**Updates to inclusion and exclusion criteria:** o Revised inclusion criterion to clarify duration of contraception requirements.<br>o • Added a new exclusion criterion on bleeding and anaemia not primarily caused by EVH. |
| Amendment 4.0, Global (21 Oct 2020)<br><br>Amendment 4.1, Local for multiple countries (11 Nov 2020) | **Global and local amendments:**<br>Removed the 100 mg starting dose of danicopan.<br>Removed one of two Follow-up Visits and established a single Follow-up Visit at approximately 30 (+ 7) days after the last dose of study intervention.<br>Updated the instructions for dose taper. |
| **Amendment Number, Type (Date)** | **Change(s) Implemented** |
| | Added text to allow enhanced pharmacokinetic (PK)/pharmacodynamic (PD) sampling and added a PK/PD table describing the blood sampling schedule and approximate blood volumes.<br>Added an exploratory objective and endpoints to characterise the PK and PD of the study intervention.<br>Removed the Fever Management Plan.<br>Revised the transfusion guidelines to recommend administering packed red blood cells when a participant has a Hgb value of < 7 g/dL (< 70 g/L), instead of < 6 g/dL (< 60 g/L).<br>Added coronavirus disease 2019 (COVID-19) risk assessment and mitigation.<br>**Updates to inclusion and exclusion criteria:**<br>o Added an inclusion criterion to allow enrollment of participants who are on a stable dose of iron, folic acid, and/or vitamin B12 supplementation.<br>o Removed the exclusion criterion that excluded participants with a Screening alkaline phosphatase result > 2 × ULN. o Introduced a cap of a maximum 30% of participants to be enrolled with < 2 transfusions 6 months prior to Screening<br>o Reduced the number of timepoints for dose escalation and simplified the dose escalation process. |
| Amendment 5.0, Global (16 Jul 2021)<br><br>Amendment 5.1, Local for multiple countries (29 Jul 2021) | **Global and Local Amendments:**<br>• Laboratory sampling text added to allow for flexibility.<br>• Instead of 30%, up to approximately 40% of participants with < 2 transfusions in the prior 6 months to be enrolled in the study.<br>• Provisions for the interim analysis revised.<br>• Revised the statistical method used for the secondary analyses.<br>• Added appendix on COVID-19 Vaccine Risk Assessment.<br>**Clarifications in inclusion/exclusion criteria and stopping criteria:**<br>o Participants with iron overload and liver enzyme abnormalities.<br>o Participants on concomitant steroids and other immunosuppressants.<br>o C5 inhibition dose frequency changes for participant convenience. |

| | |
|---|---|
| Amendment 6.0, Global (25 Feb 2022)<br><br>Amendment 6.1, Local for multiple countries (25 Feb 2022)<br><br><br><br>Amendment 6.2, Local for multiple countries (30 March 2022) | **Amendments 6.0, 6.1, and 6.2:**<br>Additional secondary objectives and endpoints.<br>Extension of the Long-term Extension (LTE) period to 2 years.<br>Addition of Section 6.7 on dose interruptions.<br>Updates to the statistical sections to reflect these changes.<br>**Updates in inclusion criteria:**<br>o Transfusion requirement prior to start of study removed.<br>o Neutrophil count threshold changed from ⩾ 750/µL to ⩾ 500/µL.<br>**Minor change to Amendment 6.2:**<br>Omission on ravulizumab administration was corrected. |
| Amendment 6.3 (US only) (08 Aug 2022) | • Based on US FDA feedback, updated primary efficacy analysis to the treatment group difference between danicopan and placebo Hgb change from Baseline to Week 12, conducted via a rerandomisation test at a 2-sided 0.05 significance level.<br>• The MMRM analysis will be reported as a sensitivity analysis.<br>• Changes in Hgb in the Per-Protocol Population will be a supportive analysis for the primary efficacy endpoint. |

Protocol deviations

In the Interim Safety Analysis Set, important deviations were reported by 41.1% of participants.

**Table 36: Important Protocol Deviations – Interim Safety Analysis Set**

| | Danicopan N = 49 n (%) | Placebo N = 24 n (%) | Total N = 73 n (%) |
|---|---|---|---|
| Participants with important deviations | 20 (40.8) | 10 (41.7) | 30 (41.1) |
| Type of important deviations | | | |
| Concomitant Medication | 2 (4.1) | 1 (4.2) | 3 (4.1) |
| Informed Consent | 3 (6.1) | 3 (12.5) | 6 (8.2) |
| Investigation Product | 6 (12.2) | 3 (12.5) | 9 (12.3) |
| Laboratory Assessment | 7 (14.3) | 0 | 7 (9.6) |
| Randomization | 3 (6.1) | 5 (20.8) | 8 (11.0) |
| Study Procedures/Tests | 7 (14.3) | 4 (16.7) | 11 (15.1) |

- **Baseline data**

**Table 37: Demographics**

| | Interim Analysis 2 Interim Efficacy Analysis Set 20 Sep 2022 (N = 63) | | | Interim Analysis 3 Randomised/Safety Set 31 Mar 2023 (N = 86) | | |
|---|---|---|---|---|---|---|
| | **Danicopan N = 42** | **Placebo N = 21** | **Total N = 63** | **Danicopan N = 57** | **Placebo N = 29** | **Total N = 86** |
| **Sex, n (%)** | | | | | | |
| Male | 19 (45.2) | 7 (33.3) | 26 (41.3) | 23 (40.4) | 9 (31.0) | 32 (37.2) |
| Female | 23 (54.8) | 14 (66.7) | 37 (58.7) | 34 (59.6) | 20 (69.0) | 54 (62.8) |
| **Race, n (%)** | | | | | | |
| American Indian or Alaska Native | 1 (2.4) | 0 | 1 (1.6) | 1 (1.8) | 0 | 1 (1.2) |
| Asian | 18 (42.9) | 7 (33.3) | 25 (39.7) | 22 (38.6) | 10 (34.5) | 32 (37.2) |

| | Interim Analysis 2 Interim Efficacy Analysis Set 20 Sep 2022 (N = 63) | | | Interim Analysis 3 Randomised/Safety Set 31 Mar 2023 (N = 86) | | |
|---|---|---|---|---|---|---|
| | **Danicopan N = 42** | **Placebo N = 21** | **Total N = 63** | **Danicopan N = 57** | **Placebo N = 29** | **Total N = 86** |
| Black or African American | 1 (2.4) | 0 | 1 (1.6) | 2 (3.5) | 0 | 2 (2.3) |
| White | 19 (45.2) | 9 (42.9) | 28 (44.4) | 28 (49.1) | 14 (48.3) | 42 (48.8) |
| Other | 1 (2.4) | 0 | 1 (1.6) | 1 (1.8) | 0 | 1 (1.2) |
| Not reported | 2 (4.8) | 4 (19.0) | 6 (9.5) | 3 (5.3) | 4 (13.8) | 7 (8.1) |
| Unknown | 0 | 1 (4.8) | 1 (1.6) | 0 | 1 (3.4) | 1 (1.2) |
| **Ethnicity, n (%)** | | | | | | |
| Hispanic or Latino | 4 (9.5) | 0 | 4 (6.3) | 6 (10.5) | 1 (3.4) | 7 (8.1) |
| Not Hispanic or Latino | 34 (81.0) | 17 (81.0) | 51 (81.0) | 46 (80.7) | 24 (82.8) | 70 (81.4) |
| Not reported | 4 (9.5) | 4 (19.0) | 8 (12.7) | 5 (8.8) | 4 (13.8) | 9 (10.5) |
| **Age (years) at informed consent** | | | | | | |
| Mean (SD) | 55.0 (15.64) | 53.1 (14.27) | 54.3 (15.11) | 52.8 (17.00) | 52.9 (14.34) | 52.8 (16.07) |
| Median | 57.5 | 53.0 | 57.0 | 56.0 | 53.0 | 54.0 |
| Min, max | 25, 80 | 29, 75 | 25, 80 | 20, 82 | 29, 77 | 20, 82 |
| **Age group (years) at informed consent** | | | | | | |
| < 65 | 30 (71.4) | 17 (81.0) | 47 (74.6) | 41 (71.9) | 23 (79.3) | 64 (74.4) |
| ≥ 65 | 12 (28.6) | 4 (19.0) | 16 (25.4) | 16 (28.1) | 6 (20.7) | 22 (25.6) |
| 65 - 74 | 7 (16.7) | 3 (14.3) | 10 (15.9) | 9 (15.8) | 4 (13.8) | 13 (15.1) |
| 75 - 84 | 5 (11.9) | 1 (4.8) | 6 (9.5) | 7 (12.3) | 2 (6.9) | 9 (10.5) |
| **BMI ($kg/m^2$)** | | | | | | |
| Mean (SD) | 26.737 (5.3766) | 24.769 (4.8660) | 26.081 (5.2563) | 25.984 (5.3183) | 24.592 (4.3398) | 25.515 (5.0276) |
| Median | 25.737 | 23.474 | 24.558 | 24.505 | 24.484 | 24.494 |
| Min, max | 19.67, 49.26 | 18.37, 37.10 | 18.37, 49.26 | 18.56, 49.26 | 18.37, 37.10 | 18.37, 49.26 |
| **Japanese participants** | | | | | | |
| No | 37 (88.1) | 19 (90.5) | 56 (88.9) | 49 (86.0) | 25 (86.2) | 74 (86.0) |
| Yes | 5 (11.9) | 2 (9.5) | 7 (11.1) | 8 (14.0) | 4 (13.8) | 12 (14.0) |
| **Transfusion history** | | | | | | |
| ≤ 2 transfusions within 6 months of Screening | 24 (57.1) | 13 (61.9) | 37 (58.7) | 33 (57.9) | 17 (58.6) | 50 (58.1) |
| > 2 transfusions within 6 months of Screening | 18 (42.9) | 8 (38.1) | 26 (41.3) | 24 (42.1) | 12 (41.4) | 36 (41.9) |
| **Screening Hgb level** | | | | | | |
| < 8.5 g/dL | 26 (61.9) | 14 (66.7) | 40 (63.5) | 35 (61.4) | 17 (58.6) | 52 (60.5) |
| ≥ 8.5 g/dL | 16 (38.1) | 7 (33.3) | 23 (36.5) | 22 (38.6) | 12 (41.4) | 34 (39.5) |

**Table 38: Selected Baseline Disease Characteristics**

| | Interim Analysis 2 Interim Efficacy Analysis Set 20 Sep 2022 (N = 63) | | | Interim Analysis 3 Randomised/Safety Set 31 Mar 2023 (N = 86) | | |
|---|---|---|---|---|---|---|
| | **Danicopan N = 42** | **Placebo N = 21** | **Total N = 63** | **Danicopan N = 57** | **Placebo N = 29** | **Total N = 86** |
| **Age (years) at PNH diagnosis** | | | | | | |
| n | 42 | 21 | 63 | 57 | 29 | 86 |
| Mean (SD) | 44.20 (16.588) | 40.79 (16.304) | 43.06 (16.442) | 43.34 (17.296) | 42.36 (16.267) | 43.00 (16.867) |
| Median | 45.00 | 41.00 | 43.60 | 40.60 | 43.40 | 41.95 |
| Min, max | 11.6, 76.4 | 18.0, 69.8 | 11.6, 76.4 | 11.6, 76.4 | 18.0, 72.7 | 11.6, 76.4 |
| **Years from diagnosis to informed consent** | | | | | | |
| n | 42 | 21 | 63 | 57 | 29 | 86 |
| Mean (SD) | 11.28 (10.593) | 12.78 (10.422) | 11.78 (10.476) | 9.95 (9.660) | 10.97 (9.479) | 10.29 (9.556) |
| Median | 7.30 | 10.80 | 8.80 | 6.80 | 9.30 | 7.25 |
| Min, max | 0.9, 49.6 | 1.2, 39.6 | 0.9, 49.6 | 0.9, 49.6 | 1.2, 39.6 | 0.9, 49.6 |
| **Age (years) at first C5 inhibitor infusion** | | | | | | |
| n | 42 | 21 | 63 | 57 | 29 | 86 |
| Mean (SD) | 50.05 (15.323) | 47.05 (14.568) | 49.05 (15.025) | 48.26 (16.621) | 47.36 (14.813) | 47.96 (15.952) |
| Median | 53.45 | 47.60 | 50.60 | 49.90 | 46.30 | 47.70 |
| Min, max | 20.9, 76.9 | 20.5, 70.4 | 20.5, 76.9 | 19.5, 76.9 | 20.5, 74.1 | 19.5, 76.9 |
| **Duration (years) from initial C5 inhibitor to first dose of study intervention** | | | | | | |
| n | 42 | 21 | 63 | 57 | 29 | 86 |
| Mean (SD) | 5.53 (3.894) | 6.66 (4.620) | 5.90 (4.147) | 5.13 (3.599) | 6.11 (4.219) | 5.46 (3.823) |
| Median | 4.31 | 5.22 | 4.53 | 4.26 | 4.65 | 4.35 |
| Min, max | 0.8, 15.8 | 0.7, 16.8 | 0.7, 16.8 | 0.6, 15.8 | 0.7, 16.8 | 0.6, 16.8 |
| **Duration (years) from start of current C5 inhibitor to first dose of study intervention** | | | | | | |
| n | 42 | 21 | 63 | 57 | 29 | 86 |
| Mean (SD) | 3.94 (3.268) | 4.54 (3.966) | 4.14 (3.496) | 3.69 (3.081) | 4.32 (3.624) | 3.90 (3.266) |
| Median | 3.57 | 3.74 | 3.66 | 3.32 | 3.66 | 3.49 |
| Min, max | 0.5, 14.2 | 0.7, 16.8 | 0.5, 16.8 | 0.5, 14.2 | 0.7, 16.8 | 0.5, 16.8 |
| **Current C5 inhibitor, n (%)** | | | | | | |
| n | 42 | 21 | 63 | 57 | 29 | 86 |
| Ravulizumab | 27 (64.3) | 10 (47.6) | 37 (58.7) | 36 (63.2) | 15 (51.7) | 51 (59.3) |
| Eculizumab | 15 (35.7) | 11 (52.4) | 26 (41.3) | 21 (36.8) | 14 (48.3) | 35 (40.7) |
| **Hgb at Baseline (g/dL)** | | | | | | |
| n | 42 | 21 | 63 | 57 | 29 | 86 |
| Mean (SD) | 7.66 (0.939) | 7.74 (1.035) | 7.69 (0.964) | 7.67 (0.947) | 7.89 (1.011) | 7.75 (0.969) |
| Median | 7.75 | 7.80 | 7.80 | 7.80 | 8.00 | 7.80 |

| | Interim Analysis 2 Interim Efficacy Analysis Set 20 Sep 2022 (N = 63) | | | Interim Analysis 3 Randomised/Safety Set 31 Mar 2023 (N = 86) | | |
|---|---|---|---|---|---|---|
| | **Danicopan N = 42** | **Placebo N = 21** | **Total N = 63** | **Danicopan N = 57** | **Placebo N = 29** | **Total N = 86** |
| Min, max | 5.7, 9.4 | 5.4, 9.3 | 5.4, 9.4 | 5.5, 9.4 | 5.4, 9.3 | 5.4, 9.4 |
| **FACIT-Fatigue scores at Baseline** | | | | | | |
| n | 42 | 21 | 63 | 56 | 28 | 84 |
| Mean (SD) | 33.46 (11.089) | 33.86 (10.781) | 33.59 (10.902) | 34.02 (11.265) | 31.68 (10.995) | 33.24 (11.165) |
| Median | 36.00 | 37.00 | 37.00 | 36.00 | 32.00 | 35.00 |
| Min, max | 9.0, 51.0 | 12.0, 52.0 | 9.0, 52.0 | 6.0, 52.0 | 12.0, 52.0 | 6.0, 52.0 |
| **Absolute reticulocyte count at Baseline ($10^9$/L)** | | | | | | |
| n | 42 | 20 | 62 | 57 | 28 | 85 |
| Mean (SD) | 236.37 (91.381) | 240.64 (120.279) | 237.75 (100.612) | 247.62 (97.187) | 222.68 (115.356) | 239.40 (103.504) |
| Median | 211.95 | 209.85 | 210.80 | 221.00 | 191.80 | 211.30 |
| Min, max | 109.4, 529.5 | 104.2, 541.9 | 104.2, 541.9 | 109.4, 529.5 | 39.4, 541.9 | 39.4, 541.9 |
| **PNH clone size at Baseline** | | | | | | |
| **Total PNH RBC clone size (Type II + Type III) (%)** | | | | | | |
| n | 14 | 9 | 23 | 26 | 17 | 43 |
| Mean (SD) | 51.621 (25.3790) | 65.511 (29.5996) | 57.057 (27.3356) | 56.804 (27.7079) | 52.512 (30.9830) | 55.107 (28.7608) |
| Median | 51.500 | 69.600 | 60.500 | 62.150 | 52.900 | 55.700 |
| Min, max | 14.10, 87.80 | 19.30, 100.00 | 14.10, 100.00 | 11.10, 99.10 | 6.80, 100.00 | 6.80, 100.00 |
| **PNH RBC Type III clone size (%)** | | | | | | |
| n | 24 | 10 | 34 | 39 | 17 | 56 |
| Mean (SD) | 47.546 (22.1639) | 51.680 (29.0473) | 48.762 (24.0030) | 48.938 (25.1011) | 46.224 (28.2960) | 48.114 (25.8810) |
| Median | 49.000 | 47.200 | 47.200 | 45.400 | 46.600 | 46.000 |
| Min, max | 11.60, 92.70 | 17.10, 99.90 | 11.60, 99.90 | 11.00, 97.30 | 6.70, 99.90 | 6.70, 99.90 |
| **PNH RBC Type II clone size (%)** | | | | | | |
| n | 14 | 8 | 22 | 26 | 15 | 41 |
| Mean (SD) | 6.929 (12.6001) | 6.063 (5.3109) | 6.614 (10.3859) | 6.485 (9.9375) | 4.807 (4.8461) | 5.871 (8.4030) |
| Median | 0.800 | 5.950 | 1.200 | 1.300 | 2.400 | 1.700 |
| Min, max | 0.10, 36.80 | 0.10, 14.50 | 0.10, 36.80 | 0.10, 36.80 | 0.10, 14.50 | 0.10, 36.80 |
| **PNH granulocyte clone size (%)** | | | | | | |
| n | 29 | 10 | 39 | 40 | 18 | 58 |
| Mean (SD) | 94.597 (9.5916) | 96.620 (4.9150) | 95.115 (8.6204) | 95.353 (8.3844) | 93.867 (8.5657) | 94.891 (8.3942) |
| Median | 98.200 | 98.300 | 98.200 | 98.600 | 96.500 | 98.200 |
| Min, max | 63.50, 100.00 | 83.70, 100.00 | 63.50, 100.00 | 63.50, 100.00 | 68.40, 100.00 | 63.50, 100.00 |

| | Interim Analysis 2 Interim Efficacy Analysis Set 20 Sep 2022 (N = 63) | | | Interim Analysis 3 Randomised/Safety Set 31 Mar 2023 (N = 86) | | |
|---|---|---|---|---|---|---|
| | **Danicopan N = 42** | **Placebo N = 21** | **Total N = 63** | **Danicopan N = 57** | **Placebo N = 29** | **Total N = 86** |
| **LDH at Baseline (U/L)** | | | | | | |
| n | 42 | 20 | 62 | 56 | 28 | 84 |
| Mean (SD) | 298.73 (105.707) | 278.25 (68.404) | 292.12 (95.189) | 304.00 (123.600) | 286.40 (93.138) | 298.13 (114.082) |
| Median | 261.00 | 257.25 | 261.00 | 261.00 | 263.00 | 261.00 |
| Min, max | 165.5, 734.5 | 180.0, 404.0 | 165.5, 734.5 | 140.0, 809.0 | 139.0, 522.7 | 139.0, 809.0 |

Medical history

A total of 72 (98.6%) of participants experienced PNH symptoms at any time prior to informed consent. The most frequent (reported in > 30% of participants) PNH symptoms were fatigue or asthenia, red or dark urine, shortness of breath (dyspnea), jaundice, and abdominal pain. The most frequent PNH-associated conditions were anaemia, hematuria or hemoglobinuria, and aplastic anaemia.

The medical/surgical history and baseline physical examination findings were comparable between the treatment groups and consistent with entry criteria and target population. The most frequently reported conditions and procedures (reported in ≥ 10% of participants) included hypertension, cholelithiasis, fatigue, anaemia, and aplastic anaemia.

A total of 85 (98.8%) participants in the Randomised/Safety Set (N = 86) experienced PNH symptoms at any time prior to informed consent. The most frequent (reported in > 30% of participants) PNH symptoms were fatigue or asthenia, red or dark urine, shortness of breath (dyspnea), jaundice (yellowing of skin or eyes), and abdominal pain (Data cut 31Mar2023). The most frequent PNH-associated conditions were anaemia, hematuria or hemoglobinuria, and aplastic anaemia.

Transfusion history

**Table 39: Packed Red Blood Cell Transfusions During 24 Weeks and 12 Weeks Prior to First Dose of Study Intervention**

| **Variable Category** | **Interim Analysis 2 Interim Efficacy Analysis Set 20 Sep 2022 (N = 63)** | | | **Interim Analysis 3 Randomized/Safety Set 31 Mar 2023 (N = 86)** | | |
|---|---|---|---|---|---|---|
| | **Danicopan (N = 42)** | **Placebo (N = 21)** | **Total (N = 63)** | **Danicopan N = 57** | **Placebo N = 29** | **Total N = 86** |
| **Number of participants with pRBC transfusions 6 months prior to Screening, n (%)** | 42 (100) | 21 (100) | 63 (100) | 56 (98.2) | 28 (96.6) | 84 (97.7) |
| **Number of participants with pRBC transfusions during the 24 weeks prior to first dose, n (%)** | 38 (90.5) | 17 (81.0) | 55 (87.3) | 52 (91.2) | 24 (82.8) | 76 (88.4) |
| **Number of transfusion instances within 24 weeks prior to receiving study intervention** | | | | | | |
| Mean (SD) | 2.5 (2.16) | 2.6 (2.11) | 2.6 (2.12) | 2.5 (2.01) | 2.8 (2.20) | 2.6 (2.07) |

| Variable Category | Interim Analysis 2 Interim Efficacy Analysis Set 20 Sep 2022 (N = 63) | | | Interim Analysis 3 Randomized/Safety Set 31 Mar 2023 (N = 86) | | |
|---|---|---|---|---|---|---|
| | Danicopan (N = 42) | Placebo (N = 21) | Total (N = 63) | Danicopan N = 57 | Placebo N = 29 | Total N = 86 |
| Median | 2.0 | 3.0 | 2.0 | 2.0 | 3.0 | 2.0 |
| Min, max | 0, 8 | 0, 8 | 0, 8 | 0, 8 | 0, 8 | 0, 8 |
| **Number of units transfused within 24 weeks prior to receiving study intervention** | | | | | | |
| Mean (SD) | 4.3 (4.66) | 4.4 (3.79) | 4.3 (4.36) | 4.1 (4.28) | 4.5 (4.06) | 4.2 (4.19) |
| Median | 2.0 | 4.0 | 3.0 | 2.0 | 4.0 | 3.0 |
| Min, max | 0, 20 | 0, 12 | 0, 20 | 0, 20 | 0, 16 | 0, 20 |
| **Number of participants with pRBC transfusions during the 12 weeks prior to first dose, n (%)** | 29 (69.0) | 15 (71.4) | 44 (69.8) | 39 (68.4) | 21 (72.4) | 60 (69.8) |
| **Number of transfusion instances within 12 weeks prior to receiving study intervention** | | | | | | |
| Mean (SD) | 1.4 (1.41) | 1.5 (1.36) | 1.4 (1.39) | 1.3 (1.34) | 1.5 (1.35) | 1.4 (1.34) |
| Median | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Min, max | 0, 6 | 0, 5 | 0, 6 | 0, 6 | 0, 5 | 0, 6 |
| **Number of units transfused within 12 weeks prior to receiving study intervention** | | | | | | |
| Mean (SD) | 2.1 (2.46) | 2.4 (2.25) | 2.2 (2.38) | 2.0 (2.31) | 2.4 (2.32) | 2.2 (2.31) |
| Median | 1.0 | 2.0 | 2.0 | 1.0 | 2.0 | 2.0 |
| Min, max | 0, 11 | 0, 7 | 0, 11 | 0, 11 | 0, 8 | 0, 11 |

Background C5 inhibitors

At study entry, 35 (40.7%) participants in the Randomised/Safety Set (N = 86) were on eculizumab and 51 (59.3%) were on ravulizumab. In the danicopan group, 36.8% were concurrently treated with eculizumab and 63.2% with ravulizumab. In the placebo group, 48.3% were on eculizumab and 51.7% were on ravulizumab.

- **Numbers analysed**

**Table 40: Analysis Sets - All Randomised Participants**

| | Danicopan N = 49 n (%) | Placebo N = 24 n (%) | Total N = 73 n (%) |
|---|---|---|---|
| Randomized | 49 (100) | 24 (100) | 73 (100) |
| Interim Safety Analysis Set[a] | 49 (100) | 24 (100) | 73 (100) |
| Interim Efficacy Analysis Set[b] | 42 (85.7) | 21 (87.5) | 63 (86.3) |
| Per-Protocol (PP) Set[c] | 42 (85.7) | 21 (87.5) | 63 (86.3) |
| Pharmacokinetic (PK) Analysis Set[d] | 48 (98.0) | 23 (95.8) | 71 (97.3) |
| Pharmacodynamic (PD) Analysis Set[d] | 49 (100) | 24 (100) | 73 (100) |

[a] The Interim Safety Analysis Set consists of all randomized participants who received at least 1 dose of study intervention (danicopan or placebo) up to interim analysis data cutoff date (28 Jun 2022).
[b] The Interim Efficacy Analysis Set consists of all randomized participants who either completed Treatment Period 1 (TP1) or discontinued from TP1.
[c] The Per-Protocol Set is a subset of the Interim Efficacy Analysis Set, without any important protocol deviations that could significantly impact efficacy analysis.
[d] The PK/PD Analysis Set includes participants who received at least 1 dose of study intervention and have evaluable PK/PD data.

- **Outcomes and estimation**

For IA1 all efficacy analyses were performed using the Interim Efficacy Analysis Set (N = 63), defined as participants who were randomly assigned to receive danicopan or placebo and reached the end of TP1 (including TP1 completers and discontinuations) by interim analysis cut-off date (28 Jun 2022). In this report, the Interim Efficacy Analysis Set is the FAS for the efficacy analysis.

During the procedure, updated efficacy data were submitted including data from two additional IAs. For IA2, all efficacy analyses were performed using the Interim Efficacy Analysis Set when all 63 participants had reached the end of TP2 (cutoff date 20 Sep 2022). For IA3, all efficacy analyses were performed on the Modified Randomised Set (N = 83), defined as all randomised participants excluding 3 participants who were randomised to the placebo group with their 12-week TP1 cut short due to early switching from placebo to danicopan following positive interim analysis readout and DMC recommendation.

Primary Evaluation Period up to Week 12 (TP1)

- ***Primary endpoint –*** *Change in Hgb from baseline to Week 12*

At IA1, using the MMRM analysis, the LS mean (SE) increase in Hgb was 29.40 (2.107) g/L in the danicopan group compared with 4.96 (3.128) g/L in the placebo group. The treatment group difference was 24.44 (3.751) g/L ($p < 0.0001$). Rerandomisation test analysis for treatment group comparison also showed the statistical significance of the treatment effect of add-on danicopan compared with placebo in the increase from baseline in Hgb ($p = 0.0007$).

Results presented below are based on the IA3 in the Modified Randomised Set.

**Table 41: Change from Baseline in Hgb (g/L) at Week 12 – Modified Randomised Set**

| Visit<br>Statistic | Danicopan<br>(N = 57)[a] | Placebo<br>(N = 25)[b] | Difference<br>(Danicopan - Placebo) | P-value |
|---|---|---|---|---|
| **Week 12** | | | | |
| LS mean (SE) | 2.814 (0.1964) | 0.413 (0.3085) | 2.402 (0.3643) | < 0.0001 (MMRM) |
| 95% CI for LS mean | 2.422, 3.206 | -0.203, 1.028 | 1.675, 3.129 | |

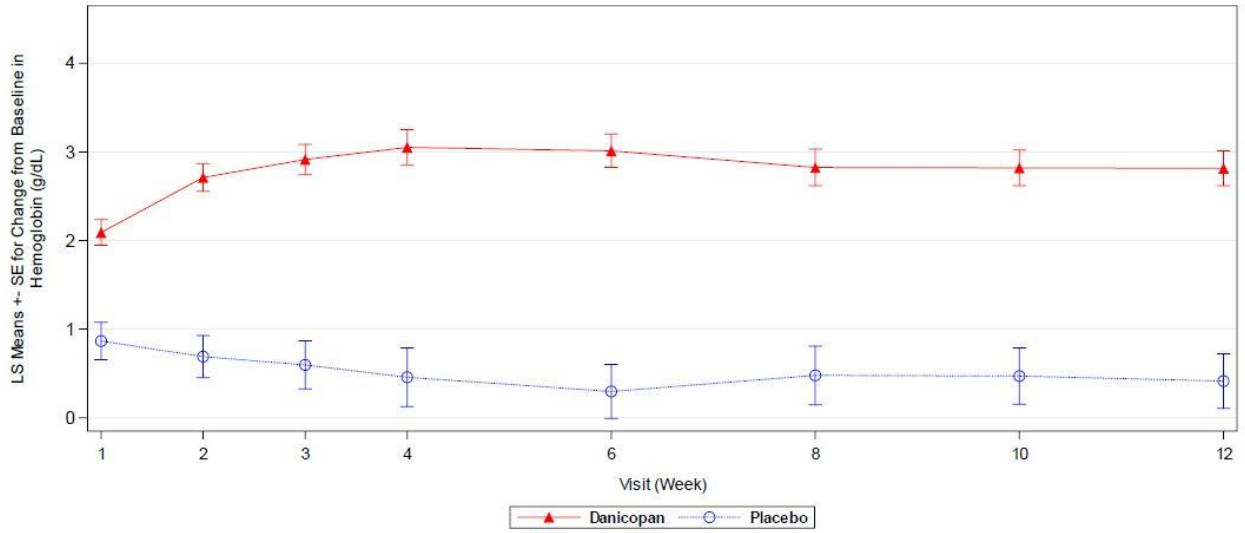
Note: Units of Hgb are expressed in g/dL. Baseline is defined as the lowest Hgb value observed between and including Screening and Day 1. The difference of LS mean is calculated as the danicopan mean minus placebo mean. MMRM includes the fixed, categorical effects of treatment group, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of Baseline Hgb value and the randomization stratification factor of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening). Unstructured covariance structure was used. P-value is from difference of LS means from the MMRM model. Hgb values collected within 4 weeks after transfusion were not included in the MMRM model.

[a] Of the 57 participants randomized to danicopan in the Modified Randomized Set, all 57 had data recorded for this outcome measure at baseline and at least 1 post-baseline visit during TP1.

[b] Of the 26 participants randomized to placebo in the Modified Randomized Set, 25 had data recorded for this outcome measure at baseline and at least 1 post-baseline visit during TP1.

Abbreviations: CI = confidence interval; Hgb = hemoglobin; MMRM = mixed-effect model for repeated measures; LS = least squares; SE = standard error; TP1 = Treatment Period 1

Data cut 31Mar2023




| Visit | W1 | W2 | W3 | W4 | W6 | W8 | W10 | W12 |
|---|---|---|---|---|---|---|---|---|
| **Difference[a] D - P (g/dL), LS mean (SE)** | 1.225 (0.2545) | 2.022 (0.2841) | 2.319 (0.3190) | 2.595 (0.3873) | 2.717 (0.3571) | 2.347 (0.3889) | 2.350 (0.3749) | 2.402 (0.3643) |

Note: Baseline is defined as the lowest Hgb value observed between and including Screening and Day 1. LS means and SE are from MMRM. Hgb values collected within 4 weeks after transfusion were not included in the MMRM.

[a] p-value < 0.0001 (MMRM analysis) for treatment difference in Hgb values at Weeks 1, 2, 3, 4, 6, 8, 10, 12.

Abbreviations: D = danicopan; Hgb = hemoglobin; LS = least squares; MMRM = mixed-effect model for repeated measures; P = placebo; SE = standard error; W = Week

Data cut 31Mar2023

**Figure 31: Plots of LS Means ± SE for Change from Baseline in Hgb During Treatment Period 1 - Modified Randomised Set**

*Sensitivity and supplemental analyses*

The Interim Efficacy Analysis Set and the Per-Protocol Set are identical; therefore, no supplemental analyses of the primary endpoint in the *Per-Protocol Set* were performed.

At IA1 sensitivity analysis for change from baseline in Hgb during TP1 using a *delta-adjustment tipping point* (imputation of missing Hgb values with various delta adjustments in a stepwise process) was

performed. This analysis (imputation of missing Hgb values with various delta adjustments in a stepwise process) demonstrated that the statistical superiority of add-on danicopan over eculizumab or ravulizumab alone is only overturned with a very large delta value adjustment (-35 g/L) used for imputation. Supplemental analysis of all Hgb values *including those collected within 4 weeks after transfusion* support the results of the primary analysis. The LS mean (SE) increase in Hgb with add-on danicopan at Week 12 was 30.30 (1.901) g/L compared with placebo which was 6.49 (2.631) g/L. The treatment group difference was 23.82 (3.236) g/L ($p < 0.0001$).

***Key secondary endpoints***

- *Proportion of Participants with an Hgb Increase of ≥ 20 g/L (≥ 2 g/dL) at Week 12 in the Absence of Transfusion*

At IA1, more than half (59.5%) of participants in the danicopan group had Hgb increase of ≥ 20 g/L at Week 12 in the absence of transfusion. No participant achieved this increase in the placebo group. The treatment group difference was statistically significant (46.9%; 95% CI: 29.16, 64.48; $p < 0.0001$).

Results presented below are based on the IA3 in the Modified Randomised Set.

**Table 42: Proportion of Participants with Hgb Increase of ≥ 20 g/L at Week 12 in the Absence of Transfusion During Treatment Period 1 – Modified Randomised Set**

| Variable<br>Statistic | Danicopan<br>(N = 57) | Placebo<br>(N = 26) | Treatment Difference<br>(Danicopan - Placebo) |
|---|---|---|---|
| **Participants with Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion** | | | |
| Number of participants (n) | 31 | 0 | NA |
| Percentage (%) | 54.4 | 0 | 46.9 |
| 95% CI | 40.66, 67.64 | 0.00, 13.23 | 31.45, 62.36 |
| Stratified CMH p-value | | | < 0.0001 |

Note: The criterion is defined as ≥ 2 g/dL increase in Hgb from Baseline to Week 12 and remaining transfusion free during the 12-week TP1. Participants who withdrew from the study early during the 12-week TP1 or have missing Hgb value at Week 12 are considered as not achieving the criterion. Percentages are based on the total number of participants in each group. The 95% CI for difference between treatment groups is produced using the Miettinen and Nurminen method. The p-value is from the CMH test controlling for stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL or ≥ 8.5 g/dL).
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Hgb = hemoglobin, NA = not applicable; TP1 = Treatment Period 1
Data cut 31Mar2023

- *Proportion of Participants with Transfusion Avoidance through Week 12%*

Participants achieved TA if they remained transfusion free and did not require a transfusion as per protocol-specified guidelines from Week 1 through Week 12. Participants who discontinued study treatment early before Week 12 were considered as not achieving TA.

At IA2 the proportion of participants with TA was 83.3% in the danicopan group compared with 38.1% in the placebo group. The treatment difference between the groups was 41.7% (95% CI: 22.67, 60.77; $p = 0.0004$).

A sensitivity analysis was conducted at IA1 using alternative handling of early discontinuations, wherein only those who discontinued from the study due to lack of efficacy during TP1 were considered as not achieving TA for TP1. Results from this supportive analysis were consistent with those of the key secondary analysis; the proportion of participants with TA in TP1 was 85.7% (95% CI: 71.46, 94.57) in the danicopan group and 42.9% (95% CI: 21.82, 65.98) in the placebo group. The treatment difference between the 2 groups was 40.5% (95% CI: 21.24, 59.66); p= 0.0006).

Results presented below are based on the IA3 in the Modified Randomised Set.

**Table 43: Proportion of Participants Achieving Transfusion Avoidance through Week 12 During Treatment Period 1 - Modified Randomised Set**

| Variable<br>Statistic | Danicopan<br>(N = 57) | Placebo<br>(N = 26) | Treatment Difference<br>(Danicopan - Placebo) |
|---|---|---|---|
| **Participants achieving pRBC/whole blood transfusion avoidance through Week 12** | | | |
| Number of participants (n) | 45 | 8 | NA |
| Percentage (%) | 78.9 | 30.8 | 46.4 |
| 95% CI | 66.11, 88.62 | 14.33, 51.79 | 29.30, 63.53 |
| Stratified CMH p-value | | | < 0.0001 |

Note: Participants who withdrew from the study during the randomized treatment period are considered as non-responders and are counted in the group requiring transfusions. Percentages are based on the total number of participants in each group. The 95% CI for difference between treatment groups is produced using the Miettinen and Nurminen method. The p-value is from the CMH test controlling for stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL or ≥ 8.5 g/dL).
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Hgb = hemoglobin; NA = not applicable; pRBC = packed red blood cells

Data cut 31Mar2023

- *Change from Baseline in FACIT-Fatigue Scores at Week 12*

At IA1 the LS mean (SE) change from Baseline in FACIT-Fatigue scores at Week 12 was 7.97 (95% CI: 5.72, 10.23) in the danicopan group and 1.85 (95% CI: -1.31, 5.02) in the placebo group, (treatment difference of 6.12 (95% CI: 2.33, 9.91), p = 0.0021).

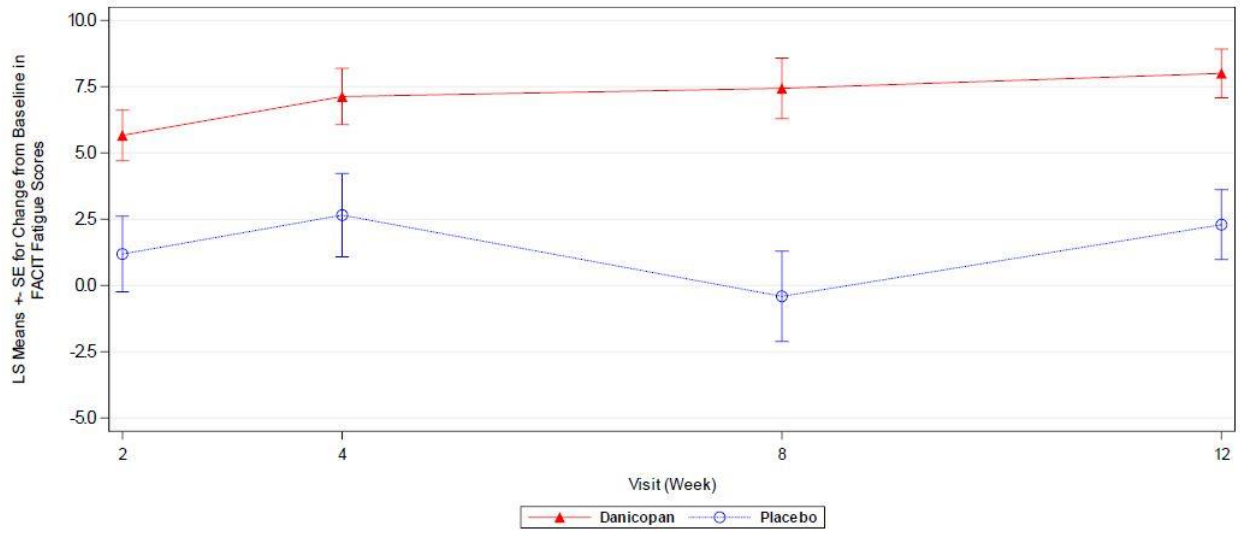
Results presented below are based on the IA3 in the Modified Randomised Set.

**Table 44: Change from Baseline in FACIT-Fatigue Scores During Treatment Period 1 Using MMRM Analysis - Modified Randomised Set**

| Visit<br>Statistic | Danicopan<br>(N = 56)[a] | Placebo<br>(N = 25)[b] | Difference<br>(Danicopan - Placebo) | P-value |
|---|---|---|---|---|
| **Week 12** | | | | |
| LS mean (SE) | 8.00 (0.917) | 2.29 (1.321) | 5.71 (1.581) | 0.0006 |
| 95% CI for LS mean | 6.18, 9.83 | -0.34, 4.93 | 2.56, 8.86 | |

Note: The difference of LS means is calculated as the danicopan mean minus placebo mean. Estimates are based on an MMRM that includes fixed, categorical effects of treatment group, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of Baseline FACIT-Fatigue scores value and the randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL or ≥ 8.5 g/dL). Unstructured covariance matrix was used. FACIT-Fatigue scores range from 0 to 52, with a higher score indicating less fatigue. The p-value is from difference of LS means from the MMRM.
[a] Of the 57 participants randomized to danicopan in the Modified Randomized Set, 56 had data recorded for this outcome measure at baseline and at least 1 post-baseline visit during TP1.
[b] Of the 26 participants randomized to placebo in the Modified Randomized Set, 25 had data recorded for this outcome measure at baseline and at least 1 post-baseline visit during TP1.
Abbreviations: CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; Hgb = hemoglobin; MMRM = mixed-effect model for repeated measures; LS = least squares; SE = standard error; TP1 = Treatment Period 1

Data cut 31Mar2023




| Visit | W2 | W4 | W8 | W12 |
|---|---|---|---|---|
| **Difference (D - P), LS mean (SE)** | 4.48 (1.689) | 4.48 (1.874) | 7.85 (2.028) | 5.71 (1.581) |

Note: Baseline is defined as the last nonmissing value prior to the first dose of study intervention. LS means and SE are from MMRM. The FACIT-Fatigue score ranges from 0 to 52, with a higher score indicating less fatigue.
Abbreviations: D = danicopan; FACIT = Functional Assessment of Chronic Illness Therapy; LS = least squares; MMRM = mixed-effect model for repeated measures; P = placebo; SE = standard error; W = Week

Source: Data cut 31Mar2023

**Figure 32: Plots of LS Means ± SE for Change from Baseline in FACIT-Fatigue Scores During Treatment Period 1 - Modified Randomised Set**

A change in score of ≥ 5 is considered clinically meaningful (Cella, 2021).

- *Change from Baseline in Absolute Reticulocyte Counts at Week 12*

At IA1 the LS mean (SE) change from baseline in absolute reticulocyte count was - 0.0838 (0.00893) × $10^{12}$/L at Week 12 in the danicopan group and 0.0035 (0.01268) × $10^{12}$/L in the placebo group. The treatment group difference was -0.0872 (95% CI: -0.1177, -0.0567) × $10^{12}$/L ($p < 0.0001$).

Results presented below are based on the IA3 in the Modified Randomised Set.

**Table 45: Change from Baseline in Absolute Reticulocyte Count During Treatment Period 1 - Interim Modified Randomized Set**

| Visit<br>Statistic | Danicopan<br>(N = 57)[a] | Placebo<br>(N = 24)[b] | Difference<br>(Danicopan - Placebo) | P-value |
|---|---|---|---|---|
| **Week 12** | | | | |
| LS mean (SE) | -93.1 (8.19) | -3.4 (12.13) | -89.6 (14.49) | < 0.0001 |
| 95% CI for LS mean | -109.4, -76.8 | -27.6, 20.7 | -118.5, -60.8 | |

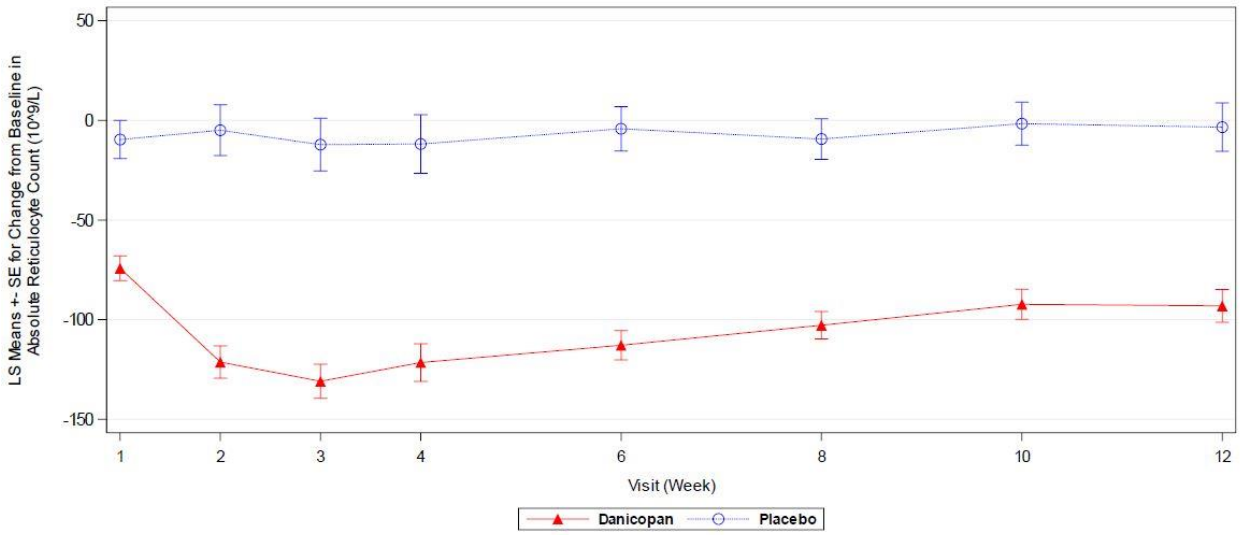
Note: Units of absolute reticulocyte count are expressed in $10^9$/L. The difference of LS means is calculated as the danicopan mean minus placebo mean. Estimates are based on an MMRM which includes categorical variables for treatment, study visit, and study visit by treatment group interaction as well as continuous covariates Baseline absolute reticulocyte count, and the randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL or ≥ 8.5 g/dL). Unstructured covariance structure was used. The p-value is from the difference of LS means from MMRM.

[a] Of the 57 participants randomized to danicopan in the Modified Randomized Set, all 57 had data recorded for this outcome measure at baseline and at least 1 post-baseline visit during TP1.

[b] Of the 26 participants randomized to placebo in the Modified Randomized Set, 24 had data recorded for this outcome measure at baseline and at least 1 post-baseline visit during TP1

Abbreviations: CI = confidence interval; Hgb = hemoglobin; MMRM = mixed-effect model for repeated measures; LS = least squares; SE = standard error; TP1 = Treatment Period 1

Data cut 31Mar2023




| Visit | W1 | W2 | W3 | W4 | W6 | W8 | W10 | W12 |
|---|---|---|---|---|---|---|---|---|
| **Difference D - P ($10^9$/L), LS mean (SE)** | -64.5 (11.26) | -116.3 (14.94) | -118.7 (15.62) | -109.6 (17.34) | -108.6 (13.22) | -93.4 (12.11) | -90.6 (13.00) | -89.6 (14.49) |

Note: Baseline is defined as the last nonmissing value prior to the first dose of study intervention. LS means and SE are from MMRM.
Abbreviations: D = danicopan; LS = least squares; MMRM = mixed-effect model for repeated measures; P = placebo; SE = standard error; W = Week

Data cut 31Mar2023

**Figure 33: Plots of LS Means ± SE for Change from Baseline in Absolute Reticulocyte Count During Treatment Period 1 - Modified Randomised Set**

All randomised paticipants

Supplemental analyses of the primary and key secondary endpoints based on **all randomized participants (N = 86)** using the same statistical methods are presented in table below.

All analyses produced consistent results with the analysis based on the Interim Efficacy Set (N = 63) and the analysis based on the Modified Randomized Set (N = 83).

**Table 46: Primary and Key Secondary Endpoints Analysis Based on All Randomized Participants (N = 86) (12-Week Treatment Period 1)**

| **Endpoint** | **Statistics** | **All Randomized Participants N = 86** | |
|---|---|---|---|
| | | Danicopan N = 57 | Placebo N = 29 |
| Hgb (g/dL) change from Baseline to Week 12 | LS Mean (SE) | 2.808 (0.1957) | 0.462 (0.3018) |
| | LS Mean Diff [95% CI] | 2.346 [1.631, 3.061] | |
| | p-value | < 0.0001 | |
| Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion | n (%)* | 31 (54.4) | 0 (0) |
| | Proportion Diff [95% CI] | 47.5 [32.63, 62.39] | |
| | p-value | < 0.0001 | |
| Transfusion avoidance during 12-week TP1 | n (%)* | 45 (78.9) | 8 (27.6) |
| | Proportion Diff [95% CI] | 48.4 [31.79, 64.94] | |
| | p-value | < 0.0001 | |
| FACIT-Fatigue score change from Baseline to Week 12 | LS Mean (SE) | 8.10 (0.916) | 2.38 (1.292) |
| | LS Mean Diff [95% CI] | 5.72 [2.62, 8.83] | |
| | p-value | 0.0004 | |
| Reticulocyte count ($10^9$/L) change from Baseline to Week 12 | LS Mean (SE) | -92.6 (8.16) | -0.9 (11.84) |
| | LS Mean Diff [95% CI] | -91.6 [-120.0, -63.3] | |
| | p-value | < 0.0001 | |

*Number and % of participants achieving the endpoint criteria out of all randomized participants in each treatment group.
Abbreviations: CI = confidence interval; Diff = difference; FACIT = Functional Assessment of Chronic Illness Therapy; Hgb = hemoglobin; LS = least squares; SE = standard error; TP1 = Treatment Period 1
Source: Data cutoff 31Mar2023

***Other secondary endpoints***

- *Change in the Number of RBC Units Transfused and Transfusion Instances Comparing 12 Weeks of Danicopan Treatment with Placebo*

**Table 47: Change in the Number of RBC Units Transfused and Transfusion Instances from 12 Weeks Prior to Treatment Initiation to Post 12 Weeks of Treatment - Interim Efficacy Analysis Set (IA1)**

| Variable Statistic | Danicopan N = 42 | Placebo N = 21 | Difference in LS Means (Danicopan – Placebo) |
|---|---|---|---|
| Number of RBC units transfused | | | |
| LS mean (SE) | -1.48 (0.261) | -0.27 (0.369) | -1.22 (0.452) |
| 95% CI for LS mean | -2.01, -0.96 | -1.01, 0.47) | -2.12, -0.31 |
| p-value | | | 0.0092 |
| Number of transfusion instances | | | |
| LS mean (SE) | -0.92 (0.169) | -0.25 (0.239) | -0.67 (0.293) |
| 95% CI for LS mean | -1.26, -0.58 | -0.73, 0.23 | -1.26, -0.08 |
| p-value | | | 0.0256 |

Note: Estimates are based on ANCOVA that includes treatment group and transfusion units/instances from 12 weeks prior to initiation of treatment p-value from ANCOVA for treatment comparison.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; RBC = red blood cell; SE = standard error

Compared to the 12 weeks prior to initiation of treatment, transfusion burden in the 12 weeks post initiation of treatment was reduced in the danicopan group but not in the placebo group. In the danicopan group, actual mean (SD) change from prior 12 weeks to post 12 weeks of treatment initiation was -0.9 (1.41) and -1.4 (2.61) in number of transfusion instances and RBC units transfused, respectively. In the placebo group, actual mean (SD) change from prior 12 weeks to post 12 weeks of treatment initiation was -0.3 (1.10) and -0.4 (1.36), respectively.

**Table 48: Change in the Number of RBC Units Transfused and Transfusion Instances from 12 Weeks Prior to Treatment Initiation to Post 12 Weeks of Treatment – Modified Randomized Set (IA3)**

| Variable Statistic | Danicopan N = 57 | Placebo N = 26 | Difference (Danicopan – Placebo) |
|---|---|---|---|
| **Number of RBC units transfused** | | | |
| LS mean (SE) | -1.40 (0.213) | -0.08 (0.316) | -1.32 (0.382) |
| 95% CI for LS mean | -1.83, -0.98 | -0.71, 0.55 | -2.08, -0.57 |
| p-value | | | 0.0008 |
| **Number of transfusion instances** | | | |
| LS mean (SE) | -0.89 (0.137) | -0.12 (0.203) | -0.77 (0.246) |
| 95% CI for LS mean | -1.17, -0.62 | -0.53, 0.28 | -1.26, -0.28 |
| p-value | | | 0.0024 |

- *Change from Baseline in Total and Direct Bilirubin at Week 12*

**Table 49: Change from Baseline in Total Bilirubin and Direct Bilirubin During 12 Weeks of Treatment Period 1 - Interim Efficacy Analysis Set (IA1)**

| Visit Statistic | Total Bilirubin (µmol/L) | | | | Direct Bilirubin (µmol/L) | | | |
|---|---|---|---|---|---|---|---|---|
| | Danicopan N = 42 | Placebo N = 21 | Difference (Danicopan – Placebo) | p-value | Danicopan N = 42 | Placebo N = 21 | Difference (Danicopan – Placebo) | p-value |
| **Week 12** | | | | | | | | |
| LS mean (SE) | -9.77 (1.692) | -2.15 (2.377) | -7.62 (2.869) | 0.0101 | -2.88 (0.357) | 0.30 (0.503) | -3.18 (0.603) | < 0.0001 |
| 95% CI for LS mean | -13.15, -6.39 | -6.90, 2.60 | -13.36, -1.88 | | -3.60, -2.17 | -0.71, 1.30 | -4.39, -1.97 | |

Note: The difference of LS means is calculated as the danicopan mean minus placebo mean. Baseline is defined as the last nonmissing value prior to first dose of study intervention. Estimates are based on MMRM that includes treatment group, the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 85 g/L and ≥ 85 g/L), Baseline total/direct bilirubin, study visit, and study visit by treatment group interaction. Unstructured covariance structure was used. P-values are from testing treatment difference of MMRM.

Abbreviations: CI = confidence interval; LS = least squares; MMRM = mixed-effect model for repeated measures; SE = standard error

**Table 50: Change from Baseline in Total Bilirubin and Direct Bilirubin at Week 12 – Modified Randomized Set**

| Visit Statistic | Total Bilirubin | | | | Direct Bilirubin | | | |
|---|---|---|---|---|---|---|---|---|
| | Danicopan N = 57 | Placebo N = 26 | Difference (Danicopan – Placebo) | p-value | Danicopan N = 57 | Placebo N = 26 | Difference (Danicopan - Placebo) | p-value |
| **Week 12** | | | | | | | | |
| LS mean (SE) | -11.51 (1.533) | -1.83 (2.215) | -9.68 (2.663) | 0.0005 | -2.82 (0.313) | -0.03 (0.454) | -2.79 (0.542) | < 0.0001 |
| 95% CI for LS mean | -14.56, -8.46 | -6.24, 2.58 | -14.98, -4.37 | | -3.44, -2.20 | -0.93, 0.88 | -3.88, -1.71 | |

Note: Units of total and direct bilirubin are expressed in µmol/L. The difference of LS means is calculated as the danicopan mean minus placebo mean. Baseline is defined as the last nonmissing value prior to first dose of study intervention. Estimates are based on MMRM that includes treatment group, the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL or ≥ 8.5 g/dL), Baseline total/direct bilirubin, study visit and study visit by treatment group interaction. Unstructured covariance structure was used. P-value is from testing treatment difference of MMRM.

Abbreviations: CI = confidence interval; Hgb = hemoglobin; LS = least squares; MMRM = mixed model for repeated measures; SE = standard error

- *Changes in PNH RBC Clone Size and C3 Fragment Deposition on PNH RBCs at 12 Weeks of Treatment*

*Changes in PNH RBC Clone Size*

**Table 51: Change from Baseline in PNH RBC Clone Size (%) During Treatment Period 1 - Interim Efficacy Analysis Set (IA1)**

| Visit<br>Statistic | Danicopan | Placebo | Difference<br>(Danicopan – Placebo) | p-value |
|---|---|---|---|---|
| **Total PNH RBC Clone Size (Type II + Type III)** | | | | |
| **Week 12** | **N = 14[a]** | **N = 8[a]** | **NA** | |
| LS mean (SE) | 24.60 (4.180) | -3.04 (5.864) | 27.63 (6.913) | 0.0010 |
| 95% CI for LS mean | 15.78, 33.42 | -15.32, 9.25 | 13.03, 42.24 | |
| **PNH RBC Type III Clone Size** | | | | |
| **Week 12** | **N = 22[a]** | **N = 9[a]** | **NA** | |
| LS mean (SE) | 26.23 (3.100) | -1.30 (5.045) | 27.54 (5.827) | < 0.0001 |
| 95% CI for LS mean | 19.86, 32.60 | -11.62, 9.01 | 15.59, 39.49 | |
| **PNH RBC Type II Clone Size** | | | | |
| **Week 12** | **N = 14[a]** | **N = 7[a]** | **NA** | |
| LS mean (SE) | -3.85 (1.613) | 3.58 (2.436) | -7.43 (2.866) | 0.0185 |
| 95% CI for LS mean | -7.24, -0.46 | -1.51, 8.68 | -13.46, -1.40 | |

Note: The difference of LS means is calculated as the danicopan mean minus placebo mean. Baseline is defined as the last nonmissing value prior to first dose of study intervention. Estimates are based on MMRM that includes treatment group, the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 85 g/L and ≥ 85 g/L), Baseline PNH RBC clone size, study visit, and study visit by treatment group interaction. Unstructured covariance structure was used. The p-values are from testing treatment difference of MMRM.

[a] Although samples were collected, some could not be analyzed due to quality issues.

Abbreviations: CI = confidence interval; Hgb = hemoglobin; LS = least squares; MMRM = mixed-effect model for repeated measures; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SE = standard error

**Table 52: Change from Baseline in PNH RBC Clone Size at Week 12 – Modified Randomized Set**

| Visit<br>Statistic | Danicopan<br>N = 57 | Placebo<br>N = 26 | Difference<br>(Danicopan - Placebo) | p-value |
|---|---|---|---|---|
| **Total PNH RBC clone size (Type II + Type III)** | | | | |
| **Week 12** | **n = 24[a]** | **n = 15[a]** | **NA** | |
| LS mean (SE) | 24.65 (3.043) | -3.18 (3.882) | 27.83 (4.770) | < 0.0001 |
| 95% CI for LS mean | 18.47, 30.83 | -11.08, 4.71 | 18.11, 37.55 | |
| **PNH RBC Type III clone size** | | | | |
| **Week 12** | **n = 37[a]** | **n = 15[a]** | **NA** | |
| LS mean (SE) | 28.20 (2.345) | -1.07 (3.774) | 29.27 (4.401) | < 0.0001 |
| 95% CI for LS mean | 23.48, 32.92 | -8.66, 6.52 | 20.41, 38.14 | |

Note: Units of PNH RBC clone size are expressed in %. The difference of LS means is calculated as the danicopan mean minus placebo mean. Baseline is defined as the last nonmissing value prior to first dose of study intervention. Estimates are based on MMRM that includes treatment group, the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL or ≥ 8.5 g/dL), Baseline PNH RBC clone size, study visit, and study visit by treatment group interaction. Unstructured covariance structure was used. The p-values are from testing treatment difference of MMRM.

[a] Although samples were collected, some could not be analyzed due to quality issues.

Abbreviations: CI = confidence interval; Hgb = hemoglobin; LS = least squares; MMRM = mixed-effect model for repeated measures; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SE = standard error

Data cut 31Mar2023

*Changes in C3 Fragment Deposition on PNH RBCs*

**Table 53: Change from Baseline in C3 Fragment Deposition on PNH RBCs (%) During Treatment Period 1 - Interim Efficacy Analysis Set (IA1)**

| Visit<br>Statistic | Danicopan<br>N = 22 | Placebo<br>N = 10 | Difference<br>(Danicopan – Placebo) | p-value |
|---|---|---|---|---|
| **C3d PNH Type 3 Cells** | | | | |
| **Week 12** | | | | |
| LS mean (SE) | -15.41 (2.948) | 0.79 (4.461) | -16.20 (5.232) | 0.0044 |
| 95% CI for LS mean | -21.45, -9.36 | -8.33, 9.91 | -26.91, -5.48 | |
| **MdFI C3d PNH Type 3 Cells** | | | | |
| **Week 12** | | | | |
| LS mean (SE) | -10.64 (2.298) | 3.25 (3.563) | -13.89 (4.182) | 0.0026 |
| 95% CI for LS mean | -15.36, -5.92 | -4.06, 10.56 | -22.48, -5.29 | |

Note: The difference of LS means is calculated as the danicopan mean minus placebo mean. Baseline is defined as the last nonmissing value prior to first dose of study intervention. Estimates are based on MMRM that includes treatment group, the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 85 g/L and ≥ 85 g/L), Baseline C3 fragment deposition, study visit, and study visit by treatment group interaction. Unstructured covariance structure was used. The p-values are from testing treatment difference of MMRM.

Abbreviations: C3d = C3 (complement component 3) fragment deposition; CI = confidence interval; Hgb = hemoglobin; LS = least squares; MdFI = median fluorescence intensity; MMRM = mixed-effect model for repeated measures; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SE = standard error

**Table 54: Change from Baseline in C3 Fragment Deposition on PNH RBCs at Week 12 – Modified Randomized Set**

| Visit<br>Statistic | Danicopan<br>N = 57 | Placebo<br>N = 26 | Difference<br>(Danicopan - Placebo) | p-value |
|---|---|---|---|---|
| **C3d PNH Type 3 cells** | | | | |
| **Week 12** | **n = 37[a]** | **n = 16[a]** | **NA** | |
| LS mean (SE) | -18.99 (2.128) | 1.19 (3.255) | -20.18 (3.834) | < 0.0001 |
| 95% CI for LS mean | -23.26, -14.72 | -5.35, 7.73 | -27.89, -12.47 | |

Note: Units of C3 fragment deposition on PNH RBCs are expressed in %. The difference of LS means is calculated as the danicopan mean minus placebo mean. Baseline is defined as the last nonmissing value prior to first dose of study intervention. Estimates are based on MMRM that includes treatment group, the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL and ≥ 8.5 g/dL), Baseline C3 fragment deposition, study visit, and study visit by treatment group interaction. Unstructured covariance structure was used. The p-values are from testing treatment difference of MMRM.

[a] Although samples were collected, some could not be analyzed due to quality issues.

Abbreviations: C3d = C3 (complement component 3) fragment deposition; CI = confidence interval; Hgb = hemoglobin; LS = least squares; MMRM = mixed-effect model for repeated measures; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SE = standard error

Data cut 31Mar2023

- *Changes in Lactate Dehydrogenase at 12 Weeks of Treatment*

**Table 55: Change from Baseline in Lactate Dehydrogenase (U/L) During Treatment Period 1 - Interim Efficacy Analysis Set (IA1)**

| Visit<br>Statistic | Danicopan<br>N = 42 | Placebo<br>N = 20 | Difference<br>Danicopan – Placebo | p-value |
|---|---|---|---|---|
| **Week 12** | | | | |
| LS mean (SE) | -23.49 (8.287) | -2.92 (11.914) | -20.57 (14.332) | 0.1569 |
| 95% CI for LS mean | -40.08, -6.90 | -26.78, 20.93 | -49.28, 8.15 | |

Note: The difference of LS means is calculated as the danicopan mean minus placebo mean. Baseline is defined as the average of all available assessments prior to the first dose of study intervention. Estimates are based on MMRM that includes treatment group, the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 85 g/L and ≥ 85 g/L), Baseline LDH, study visit, and study visit by treatment group interaction. Unstructured covariance structure was used. P-value is from testing treatment difference of MMRM.

Abbreviations: CI = confidence interval; Hgb = hemoglobin; LDH = lactate dehydrogenase; LS = least squares; MMRM = mixed-effect model for repeated measures; SE = standard error

**Table 56: Change from Baseline in Lactate Dehydrogenase at Week 12 – Modified Randomized Set**

| Visit<br>Statistic | Danicopan<br>N = 56[a] | Placebo<br>N = 25[b] | Difference<br>Danicopan – Placebo | p-value |
|---|---|---|---|---|
| **Week 12** | | | | |
| LS mean (SE) | -25.04 (7.887) | -15.21 (11.604) | -9.82 (13.926) | 0.4835 |
| 95% CI for LS mean | -40.82, -9.25 | -38.46, 8.04 | -37.72, 18.08 | |

Note: Units of LDH are expressed in U/L. The difference of LS means is calculated as the danicopan mean minus placebo mean. Baseline is defined as the average of all available assessments prior to the first dose of study intervention. Estimates are based on MMRM that includes treatment group, the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL and ≥ 8.5 g/dL), Baseline LDH, study visit, and study visit by treatment group interaction. Unstructured covariance structure was used. LDH values in samples affected by TTH are not used in the analysis. Lab samples with serum potassium ≥ 6 mmol/L and LDH ≥ 2× ULN are defined as having TTH. P-value is from testing treatment difference of MMRM.

[a] Of the 57 participants randomized to danicopan in the Modified Randomized Set, 56 had data recorded for this outcome measure at baseline and at least 1 post-baseline visit during TP1.

[b] Of the 26 participants randomized to placebo in the Modified Randomized Set, 25 had data recorded for this outcome measure at baseline and at least 1 post-baseline visit during TP1.

Abbreviations: CI = confidence interval; Hgb = hemoglobin; LDH = lactate dehydrogenase; LS = least squares; MMRM = mixed-effect model for repeated measures; SE = standard error; TTH = table-top hemolysis; ULN = upper limit of normal

Data cut 31Mar2023

- *Percentage of Participants with Hgb Normalisation at Week 12*

**Table 57: Proportion of Participants with Hgb Normalisation at Week 12 – Interim Efficacy Analysis Set (IA1)**

| Variable<br>Statistic | Danicopan<br>N = 42 | Placebo<br>N = 21 | Treatment Difference<br>(Danicopan – Placebo) |
|---|---|---|---|
| **Achieving Hgb normalization at Week 12** | | | |
| Number of participants (n) | 12 | 0 | NA |
| Percentage | 28.6 | 0 | 18.4 |
| 95% CI | 15.72, 44.58 | 0.00, 16.11 | -0.84, 37.71 |
| Stratified CMH p-value | | | 0.0080 |

Note: Hgb normalization is defined as Hgb value above LLN reference range. Percentages are based on the total number of participants in each group. The 95% CI for difference between treatment groups are produced using the Miettinen and Nurminen method. Participants with transfusions within 4 weeks prior to Week 12 are considered as not meeting Hgb normalization regardless of actual value observed at Week 12. The p-value is from the Cochran-Mantel-Haenszel test controlling for stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 85 g/L and ≥ 85 g/L).

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Hgb = hemoglobin; LLN = lower limit of normal

**Table 58: Proportion of Participants with Hgb Normalisation at Week 12 – Modified Randomized Set**

| Variable<br>Statistic | Danicopan<br>N = 57 | Placebo<br>N = 26 | Treatment Difference<br>(Danicopan - Placebo) |
|---|---|---|---|
| **Achieving Hgb normalisation at Week 12** | | | |
| Number of participants (n) | 15 | 0 | NA |
| Percentage (%) | 26.3 | 0 | 18.4 |
| 95% CI | 15.54, 39.66 | 0.00, 13.23 | 1.84, 35.02 |
| Stratified CMH p-value | | | 0.0032 |

Note: Hgb normalization is defined as Hgb value above LLN reference range. Percentages are based on the total number of participants in each group. The 95% CI for difference between treatment groups is produced using the Miettinen and Nurminen method. Participants with transfusions within 4 weeks prior to Week 12 are considered as not meeting Hgb normalization regardless of actual value observed at Week 12. The p-value is from the Cochran-Mantel-Haenszel test controlling for stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL and ≥ 8.5 g/dL).

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Hgb = hemoglobin; LLN = lower limit of normal; NA = not applicable

Evaluation Period up to Week 24 (TP2)

***Other secondary endpoints at Week 24***

- *Change in the Number of RBC Units Transfused and Transfusion Instances at Week 24*

**Table 59: Change in the Number of RBC Units Transfused and Transfusion Instances from 24 Weeks Prior to Initiation of Treatment to Post 24 Weeks of Treatment for Participants Randomized to Danicopan Group – Interim Efficacy Analysis Set (IA1)**

| Variable Statistic | Prior 24 Weeks (24 Weeks Prior to D1) | Post 24 Weeks (24 Weeks Post D1) | Change from Prior 24 Weeks to Post 24 Weeks |
|---|---|---|---|
| **Number of RBC units transfused** | | | |
| n | 33 | 33 | 33 |
| Mean (SD) | 4.6 (5.02) | 1.2 (3.15) | -3.4 (5.80) |
| 95% CI for mean | 2.85, 6.42 | 0.10, 2.33 | -5.48, -1.37 |
| **Number of transfusion instances** | | | |
| n | 33 | 33 | 33 |
| Mean (SD) | 2.5 (2.14) | 0.7 (2.00) | -1.8 (2.61) |
| 95% CI for mean | 1.73, 3.24 | 0.02, 1.44 | -2.68, -0.83 |

Note: Prior 24 weeks: 24 weeks prior to first dose of danicopan treatment; post 24 weeks: 24 weeks after first dose of danicopan treatment

Abbreviations: CI = confidence interval; D1 = Day 1; RBC = red blood cell; SD = standard deviation

**Table 60: Change in the Number of RBC Units Transfused and Transfusion Instances from 12-Week Treatment Period 1 to 12-Week Treatment Period 2 for Participants Randomized to Placebo Group - Interim Efficacy Analysis Set (IA1)**

| Variable Statistic | 12-Week TP1 (D1 to Week 12) | 12-Week TP2 (Week 12 to Week 24) | Change from TP1 to TP2 |
|---|---|---|---|
| **Number of RBC units transfused** | | | |
| n | 16 | 16 | 16 |
| Mean (SD) | 2.1 (2.00) | 0.1 (0.50) | -2.0 (1.79) |
| 95% CI for mean | 1.06, 3.19 | -0.14, 0.39 | -2.95, -1.05 |
| **Number of transfusion instances** | | | |
| n | 16 | 16 | 16 |
| Mean (SD) | 1.3 (1.18) | 0.1 (0.25) | -1.2 (1.05) |
| 95% CI for mean | 0.62, 1.88 | -0.07, 0.20 | -1.75, -0.63 |

Abbreviations: CI = confidence interval; RBC = red blood cell; SD = standard deviation; TP1 = Treatment Period 1; TP2 = Treatment Period 2

**Table 61: Change in the Number of RBC Units Transfused and Transfusion Instances from 24 Weeks Prior to Initiation of Treatment to Post 24 Weeks of Treatment for Participants Randomized to Danicopan Group – Modified Randomized Set**

| Variable Statistic | Prior 24 Weeks (24 Weeks prior to D1) | Post 24 Weeks (24 Weeks post D1) | Change from Prior 24 Weeks to Post 24 Weeks |
|---|---|---|---|
| **Number of red blood cell (RBC) units transfused** | | | |
| n | 55 | 55 | 55 |
| Mean (SD) | 4.0 (4.34) | 1.3 (2.95) | -2.7 (4.86) |
| 95% CI for mean | 2.81, 5.16 | 0.46, 2.05 | -4.04, -1.41 |
| **Number of transfusion instances** | | | |
| n | 55 | 55 | 55 |
| Mean (SD) | 2.4 (2.00) | 0.8 (2.22) | -1.5 (2.41) |
| 95% CI for mean | 1.84, 2.92 | 0.24, 1.44 | -2.20, -0.89 |

Note: Prior 24 weeks: 24 weeks prior to first dose of danicopan treatment; post 24 weeks: 24 weeks after first dose of danicopan treatment
Abbreviations: CI = confidence interval; D1 = Day 1; RBC = red blood cell; SD = standard deviation

**Table 62: Change in the Number of RBC Units Transfused and Transfusion Instances from 12-Week Treatment Period 1 to 12-Week Treatment Period 2 for Participants Randomized to Placebo Group – Modified Randomized Set**

| Variable<br>Statistic | 12-Week TP1<br>(D1 to Week 12) | 12-Week TP2<br>(Week 12 to Week 24) | Change from TP1 to TP2 |
|---|---|---|---|
| **Number of red blood cell (RBC) units transfused** | | | |
| n | 24 | 24 | 24 |
| Mean (SD) | 2.3 (2.27) | 0.5 (1.69) | -1.8 (2.13) |
| 95% CI for mean | 1.33, 3.25 | -0.22, 1.22 | -2.69, -0.89 |
| **Number of transfusion instances** | | | |
| n | 24 | 24 | 24 |
| Mean (SD) | 1.4 (1.35) | 0.3 (1.24) | -1.0 (1.30) |
| 95% CI for mean | 0.81, 1.94 | -0.19, 0.86 | -1.59, -0.49 |

Abbreviations: CI = confidence interval; D1 = Day 1; RBC = red blood cell; SD = standard deviation; TP1 = Treatment Period 1; TP2 = Treatment Period 2

- *Percentage of Participants with Transfusion Avoidance through 24 Weeks of Treatment*

**Table 63: Proportion of Participants Achieving Transfusion Avoidance During Treatment Period 2 - Interim Efficacy Analysis Set**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 33 | PBO/DAN[b]<br>N = 16 |
|---|---|---|
| **Achieving pRBC/whole blood transfusion avoidance from Week 12 to Week 24** | | |
| Number of participants (n) | 26 | 14 |
| Percentage (%) | 78.8 | 87.5 |
| 95% CI | 61.09, 91.02 | 61.65, 98.45 |

Note: Transfusion avoidance is defined as the proportion of participants who remain transfusion free and do not require a transfusion per protocol-specified guidelines from Week 12 to Week 24. Participants who withdraw from the study during TP2 are considered as nonresponders and counted in the group requiring transfusions. Percentages are based on the total number of participants in each group. The 95% exact CIs are computed using the Clopper-Pearson method.

[a] Participants received danicopan in TP1 and continued with danicopan in TP2.

[b] Participants received placebo in TP1 and switched to danicopan in TP2.

Abbreviations: CI = confidence interval; DAN = danicopan; PBO = placebo; pRBC = packed red blood cells; TP2 = Treatment Period 2

**Table 64: Proportion of Participants Achieving Transfusion Avoidance During 24 Weeks of Treatment - Interim Efficacy Analysis Set (IA1)**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 33 |
|---|---|
| **Achieving pRBC/whole blood transfusion avoidance through Week 24** | |
| Number of participants (n) | 25 |
| Percentage (%) | 75.8 |
| 95% CI | 57.74, 88.91 |

Note: Transfusion avoidance is defined as the proportion of participants who remain transfusion free and do not require a transfusion per protocol-specified guidelines through Week 24. Participants who withdrew from the study during TP2 are considered as nonresponders and counted in the group requiring transfusions. The 95% exact CI is computed using Clopper-Pearson method.

[a] Participants received danicopan in TP1 and continued with danicopan in TP2.

Abbreviations: CI = confidence interval; DAN = danicopan; pRBC = packed red blood cells; TP1 = Treatment Period 1; TP2 = Treatment Period 2

**Table 65: Proportion of Participants Achieving Transfusion Avoidance During Treatment Period 2 – Modified Randomized Set**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 55 | PBO/DAN[b]<br>N = 24 |
|---|---|---|
| **Achieving pRBC/whole blood transfusion avoidance from Week 12 to Week 24** | | |
| Number of participants (n) | 44 | 20 |
| Percentage (%) | 80.0 | 83.3 |
| 95% CI | 67.03, 89.57 | 62.62, 95.26 |

Note: Transfusion avoidance is defined as the proportion of participants who remain transfusion free and do not require a transfusion per protocol-specified guidelines from Week 12 to Week 24. Participants who withdrew from the study during TP2 are considered as nonresponders and counted in the group requiring transfusions. Percentages are based on the total number of participants in each group. The 95% exact CIs are computed using the Clopper-Pearson method.
Participants received danicopan in TP1 and continued receiving danicopan in TP2.
Participants received placebo in TP1 and switched to danicopan in TP2.

Abbreviations: CI = confidence interval; DAN = danicopan; PBO = placebo; pRBC = packed red blood cells; TP1 = Treatment Period 1; TP2 = Treatment Period 2

**Table 66: Proportion of Participants Achieving Transfusion Avoidance During 24 Weeks of Treatment – Modified Randomized Set**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 55 |
|---|---|
| **Achieving pRBC/whole blood transfusion avoidance through Week 24** | |
| Number of participants (n) | 38 |
| Percentage (%) | 69.1 |
| 95% CI | 55.19, 80.86 |

Note: Transfusion avoidance is defined as the proportion of participants who remain transfusion free and do not require a transfusion per protocol-specified guidelines through Week 24. Participants who withdrew from the study during TP2 are considered as nonresponders and counted in the group requiring transfusions. The 95% exact CI is computed using Clopper-Pearson method.
Participants received danicopan in TP1 and continued receiving danicopan in TP2.

Abbreviations: CI = confidence interval; DAN = danicopan; pRBC = packed red blood cells; TP1 = Treatment Period 1; TP2 = Treatment Period 2

- *Change from Baseline in FACIT-Fatigue Scores at Week 24*

At Week 24, the LS mean (SE) change from Baseline in FACIT-Fatigue scores was clinically meaningful at 5.08 (1.627) in the DAN/DAN group and was 4.98 (2.357) in the PBO/DAN group (Table 67).

**Table 67: Change from Baseline in FACIT-Fatigue Scores During Treatment Period 2 - Interim Efficacy Analysis Set (IA1)**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 31 | PBO/DAN[b]<br>N = 16 |
|---|---|---|
| **Week 24** | | |
| LS mean (SE) | 5.08 (1.627) | 4.98 (2.357) |
| 95% CI for LS mean | 1.75, 8.41 | -0.17, 10.14 |

Note: Estimates are based on MMRM that includes the observed randomization stratification factors of transfusion history ( > 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 85 g/L and ≥ 85 g/L), Baseline FACIT-Fatigue scores, and study visit. Unstructured covariance structure was used. FACIT-Fatigue scores range from 0 to 52, with a higher score indicating less fatigue.

[a] Participants received danicopan in TP1 and continued with danicopan in TP2.

[b] Participants received placebo in TP1 and switched to danicopan in TP2.

Abbreviations: CI = confidence interval; DAN = danicopan; FACIT = functional assessment of chronic illness therapy; Hgb = hemoglobin; LS = least squares; MMRM = mixed-effect model for repeated measures; PBO = placebo; SE = standard error; TP = treatment period

**Table 68: Change from Baseline in FACIT-Fatigue Scores at Week 24 – Modified Randomized Set**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 52 | PBO/DAN[b]<br>N = 24 |
|---|---|---|
| **Week 24** | | |
| LS mean (SE) | 6.19 (1.043) | 6.15 (2.077) |
| 95% CI for LS mean | 4.10, 8.29 | 1.82, 10.49 |

Note: Estimates are based on MMRM that includes the observed randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and Screening Hgb (< 8.5 g/dL and ≥ 8.5 g/dL), Baseline FACIT-Fatigue scores, and study visit. Unstructured covariance structure was used. FACIT-Fatigue scores range from 0 to 52, with a higher score indicating less fatigue.

Participants received danicopan in TP1 and continued receiving danicopan in TP2.

Participants received placebo in TP1 and switched to danicopan in TP2.

Abbreviations: CI = confidence interval; DAN = danicopan; FACIT = Functional Assessment of Chronic Illness Therapy; Hgb = hemoglobin; LS = least squares; MMRM = mixed-effect model for repeated measures; PBO = placebo; SE = standard error; TP1 = Treatment Period 1; TP2 = Treatment Period 2

- *Percentage of Participants with Hgb Stabilisation during Last 12 Weeks of Treatment in Participants Receiving 24 weeks of Danicopan*

**Table 69: Proportion of Participants with Hgb Stabilisation During Treatment Period 2 - Interim Efficacy Analysis Set (IA1)**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 33 |
|---|---|
| **Achieving Hgb Stabilization from Week 12 to Week 24** | |
| Number of participants (n) | 21 |
| Percentage (%) | 63.6 |
| 95% CI | 45.12, 79.60 |

Note: Hgb stabilization is defined as avoidance of > 10 g/L decrease in Hgb levels from Week 12 to Week 24. Participants with transfusions within 4 weeks prior to Week 24 are considered as not meeting Hgb stabilization regardless of actual value observed at Week 24. The 95% exact CIs are computed using Clopper-Pearson method.

[a] Participants received danicopan in TP1 and continued on danicopan in TP2 (thus receiving danicopan for 24 weeks).

Abbreviations: CI = confidence interval; DAN = danicopan; Hgb = hemoglobin; TP = treatment period

At IA3, of the 55 participants receiving danicopan as add-on treatment in TP1 and TP2, 58.2% achieved Hgb stabilisation (defined as avoidance of > 1 g/dL decrease in Hgb level) from Week 12 to Week 24.

**Table 70: Proportion of Participants with Hgb Stabilisation During Treatment Period 2 – Modified Randomized Set**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 55 |
|---|---|
| **Achieving Hgb stabilisation from Week 12 to Week 24** | |
| Number of participants (n) | 32 |
| Percentage (%) | 58.2 |
| 95% CI | 44.11, 71.35 |

Note: Hgb stabilization is defined as avoidance of > 1 g/dL decrease in Hgb levels from Week 12 to Week 24. Participants with transfusions within 4 weeks prior to Week 24 are considered as not meeting Hgb stabilization regardless of actual value observed at Week 24. The 95% exact CIs are computed using Clopper-Pearson method.
Participants received danicopan in TP1 and continued receiving danicopan in TP2 (thus receiving danicopan for 24 weeks).
Abbreviations: CI = confidence interval; DAN = danicopan; Hgb = hemoglobin; TP1 = Treatment Period 1; TP2 = Treatment Period 2

Data cut 31Mar2023

- *Proportion of Participants with an Hgb Increase of ≥ 20 g/L (2 g/dL) at Week 24 in the Absence of Transfusion*

Of the participants receiving danicopan as add-on treatment in TP1 and TP2, 51.5% achieved clinically meaningful increase from Baseline in Hgb levels of ≥ 20 g/L at Week 24 and had no transfusions during this treatment period, indicating maintenance of clinical benefit of danicopan over 24 weeks of treatment.

**Table 71: Proportion of Participants with Hgb Increase of ≥ 20 g/L at Week 24 in the Absence of Transfusion During 24 Weeks of Treatment - Interim Efficacy Analysis Set (IA1)**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 33 |
|---|---|
| **Participants with Hgb increase of ≥ 20 g/L) at Week 24 in the absence of transfusion** | |
| Number of participants (n) | 17 |
| Percentage (%) | 51.5 |
| 95% CI | 33.54, 69.20 |

Note: The criterion is defined as ≥ 20 g/L increase in Hgb from Baseline to Week 24 and remaining transfusion free during the 24-week treatment period. Participants who withdrew from the study early during TP2 or have missing Hgb value at Week 24 are considered as not achieving the criterion. The 95% exact CIs are computed using the Clopper-Pearson method.
[a] Participants received danicopan in TP1 and continued on danicopan in TP2.
Abbreviations: CI = confidence interval; DAN = danicopan; Hgb = hemoglobin; TP = treatment period

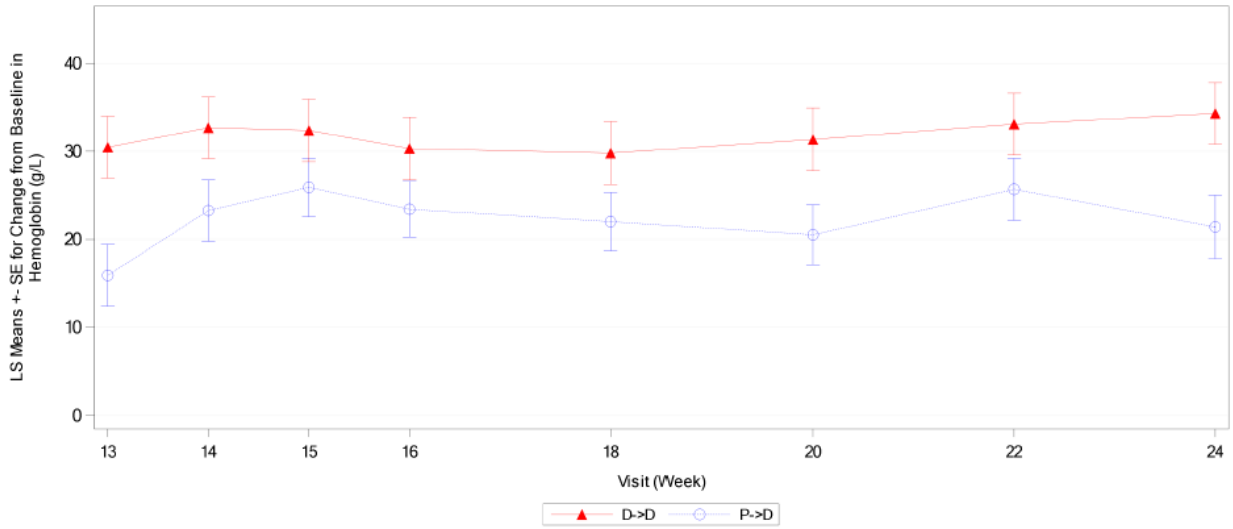
**Table 72: Proportion of Participants with Hgb Increase of ≥ 2 g/dL at Week 24 in the Absence of Transfusion During 24 Weeks of Treatment - Modified Randomized Set**

| Variable<br>Statistic | DAN/DAN[a]<br>N = 55 |
|---|---|
| **Participants with Hgb increase of ≥ 2 g/dL at Week 24 in the absence of transfusion** | |
| Number of participants (n) | 23 |
| Percentage (%) | 41.8 |
| 95% CI | 28.65, 55.89 |

Note: The criterion is defined as ≥ 2 g/dL increase in Hgb from Baseline to Week 24 and remaining transfusion free during the 24-week treatment period. Participants who withdrew from the study early during TP2 or have missing Hgb value at Week 24 are considered as not achieving the criterion. The 95% exact CIs are computed using the Clopper-Pearson method.
Participants received danicopan in TP1 and continued receiving danicopan in TP2.
Abbreviations: CI = confidence interval; DAN = danicopan; Hgb = hemoglobin; TP1 = Treatment Period 1; TP2 = Treatment Period 2

***Additional analyses at Week 24***

- *Change from Baseline in Hgb at Week 24*




Note: D->D = participants received danicopan in TP1 and continued on danicopan in TP2; P->D = participants received placebo in TP1 and switched to danicopan in TP2. Baseline is defined as the lowest Hgb value observed between and including Screening and Day 1. LS means and SE are from MMRM. Hgb values collected within 4 weeks after transfusion are not included in the MMRM.
Abbreviations: Hgb = hemoglobin; LS = least squares; MMRM = mixed model for repeated measures; SE = standard error; TP = treatment period

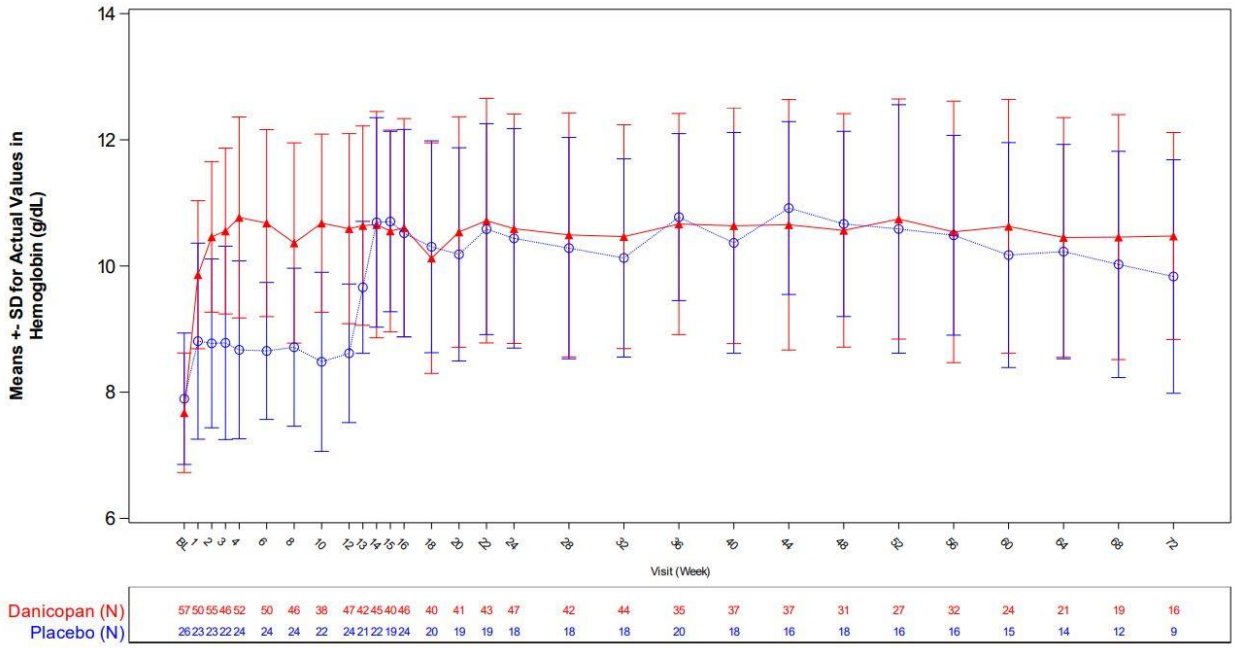
**Figure 34: Plots of LS Means ± SE for Change from Baseline in Hgb During TP2 - Interim Efficacy Analysis Set (IA1)**

At IA3 improvements in Hgb during TP1 in the danicopan group were maintained through Week 24. Participants on placebo in TP1 who switched to danicopan in TP2 (PBO/DAN group) also showed improvements in mean Hgb values from Week 13 through Week 24. At Week 24, LS mean (SE) change from Baseline in Hgb was 2.949 (0.2656) g/dL in the DAN/DAN group and 2.254 (0.2893) g/dL in the PBO/DAN group.

Long-Term Extension Period up to data cut-off

After TP2 (Week 24), participants continued to receive danicopan as an add-on treatment to ravulizumab or eculizumab during the LTE.

- *Haemoglobin level over time*




Note: Baseline is defined as the lowest Hgb value observed between and including Screening and Day 1. At Week 12, participants in the PBO/DAN group switched from placebo to danicopan in TP2 and LTE, while participants in the DAN/DAN group continued to receive danicopan in TP2 and LTE.
Abbreviations: BL = baseline; DAN = danicopan; Hgb = hemoglobin; LTE = Long-term Extension; PBO = placebo; SD = standard deviation; TP1 = Treatment Period 1; TP2 = Treatment Period 2

**Figure 35: Plots of Mean ± SD for Actual Values in Hgb Through TP1, TP2, and LTE – Modified Randomized Set**

- *FACIT-Fatigue score over time*

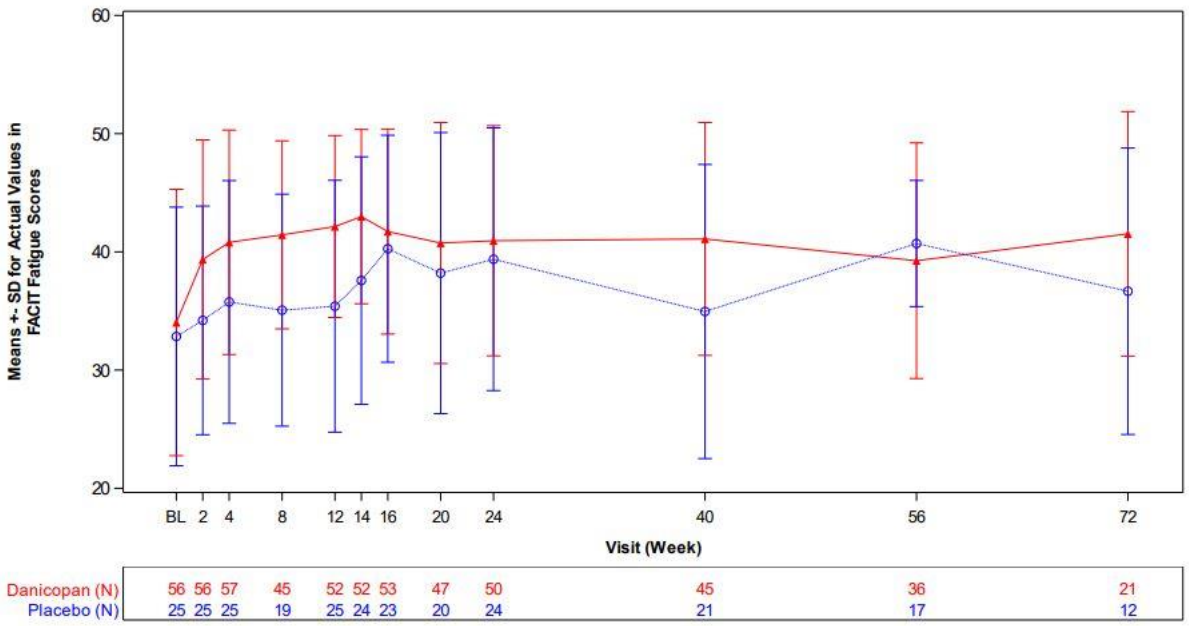
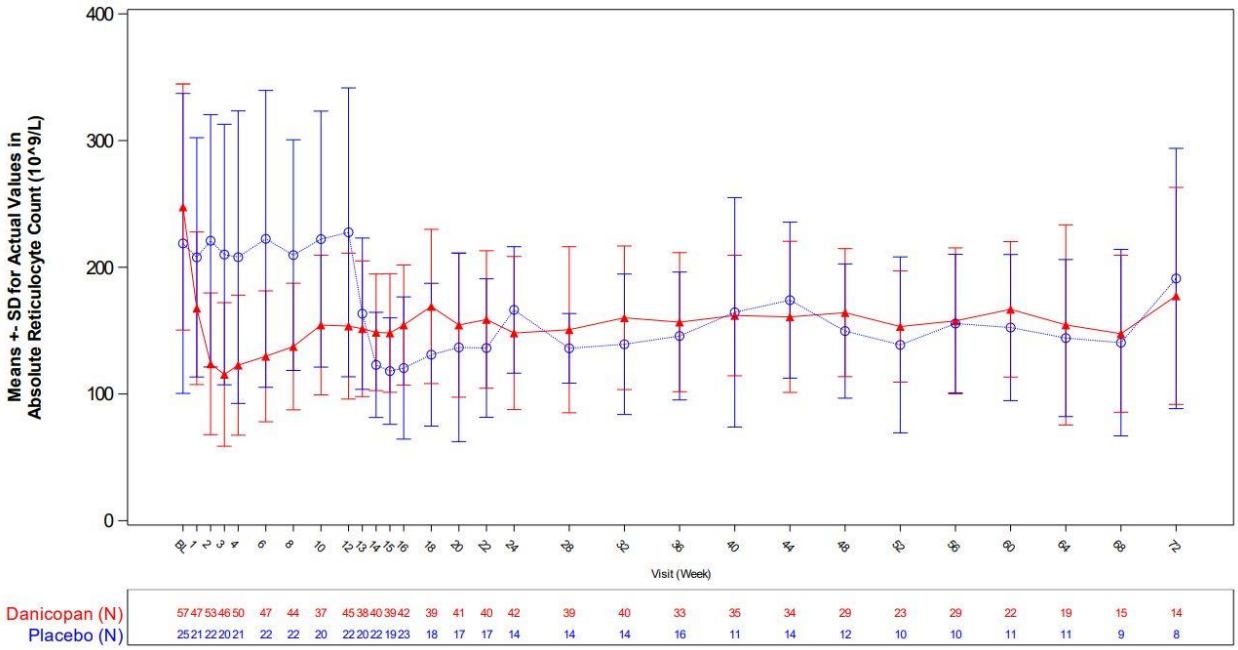



**Figure 36: Plots of Mean ± SD for Actual Values in FACIT-Fatigue Scores Through TP1, TP2, and LTE – Interim Efficacy Analysis Set**

- *Absolute reticulocyte count over time*




Note: Baseline is defined as the last nonmissing value prior to the first dose of study intervention. At Week 12, participants in the PBO/DAN group switched from placebo to danicopan in TP2 and LTE, while participants in the DAN/DAN group continued to receive danicopan in TP2 and LTE.
Abbreviations: BL = baseline; DAN= danicopan; LTE = Long-term Extension; PBO = placebo; SD = standard deviation; TP1 = Treatment Period 1; TP2 = Treatment Period 2

**Figure 37: Plots of Mean ± SD for Actual Values in Absolute Reticulocyte Count Through TP1, TP2, and LTE – Modified Randomized Set**

- **Ancillary analyses**

Subgroup analyses

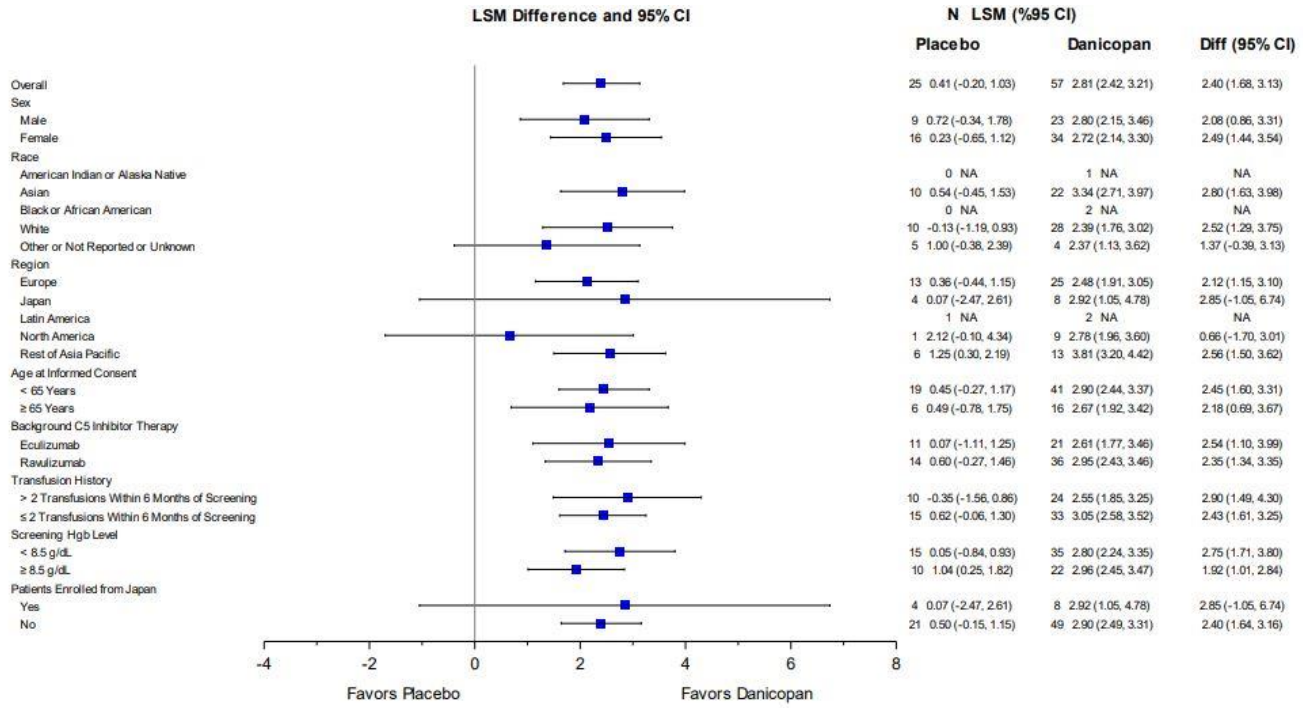



**Figure 38: Forest Plot of Change from Baseline in Haemoglobin (g/dL) During 12 Weeks of Treatment Period 1, Overall and by Subgroup (Modified Randomized Set)**

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 73: Summary of efficacy for trial ALXN2040-PNH-301**

| **Title: A Phase 3 Study of danicopan (ALXN2040) as add-on therapy to a C5 Inhibitor (eculizumab or ravulizumab) in patients with paroxysmal nocturnal haemoglobinuria who have clinically evident extravascular haemolysis (EVH)** | | | |
|---|---|---|---|
| Study identifier | ALXN2040-PNH-301; 2019-003829-18; NCT04469465 | | |
| Design | Multiple-region, randomized, double-blind, placebo-controlled, Phase 3 study. | | |
| | Duration of main phase:<br>Duration of screening phase:<br>Duration of extension phase: | | 12 weeks (Treatment Period 1)<br>45 days<br>Treatment Period 2: 12 weeks<br>Long-term Extension: up to 2 years |
| Hypothesis | Superiority | | |
| Treatments groups | Danicopan (add-on to ravulizumab or eculizumab | | The starting dose of danicopan is 150 mg three times a day (tid), The dose could be increased from 150 mg tid to 200 mg tid based on safety monitoring and haemoglobin (Hgb) levels.<br>N =42 |
| | Placebo (add-on to ravulizumab or eculizumab) | | Matching treatment<br>N=21 |
| Endpoints and definitions | Primary endpoint | Change from baseline in Hbg level at Week 12 | Change in haemoglobin relative to baseline after 12 weeks of treatment with danicopan compared with placebo |
| | Secondary | Proportion of patients with Hbg≥2 g/dL at week 12 | Proportion of patients with haemoglobin increase ≥2 g/dL at week 12 in the absence of transfusions |
| | Secondary | Tranfusion avoidance at week 12 | Proportion of patients with transfusion avoidance at week 12 |
| | Secondary | Change in FACIT-Fatigue at week 12 | Change from baseline in FACIT-Fatigue scores at week 12 |
| | Secondary | Change from baseline in ARC at week 12 | Change from baseline in absolute reticulocyte counts (ARC) at week 12 |
| Database lock | 18 Aug 2022 (data cut-off: 28 Jun 2022) | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | Intent to treat<br>Interim analysis – 12 weeks | | |
| Descriptive statistics | Treatment group | Danicopan | Placebo |

| **Title: A Phase 3 Study of danicopan (ALXN2040) as add-on therapy to a C5 Inhibitor (eculizumab or ravulizumab) in patients with paroxysmal nocturnal haemoglobinuria who have clinically evident extravascular haemolysis (EVH)** | | | | |
|---|---|---|---|---|
| Study identifier | ALXN2040-PNH-301; 2019-003829-18; NCT04469465 | | | |
| and estimate variability | Number of subject | 42 | 21 | |
| | Change from Baseline in Hgb level at Week 12 (g/dL); LS mean<br>(95%CI) | 2.94<br>(2.52, 3.36) | 0.50<br>(-0.13, 1.12) | |
| | Proportion of patients with Hbg increase of ≥ 2 g/dL (%)<br>(95%CI) | 59.5<br>(43.28, 74.37) | 0<br>(0.00, 16.11) | |
| | Transfusions avoidance (%)<br>(95%CI) | 83.3<br>(68.64, 93.03) | 38.1<br>(18.11, 61.56) | |
| | Change in FACIT-Fatigue score (Mean)<br>(95%CI) | 7.97<br>(5.72, 10.23) | 1.85<br>(-1.31, 5.02) | |
| | Change in absolute reticulocyte count (Mean)<br>(95%CI) | -83.8<br>(-101.6, 65.9) | 3.5<br>(117.7, 56.7) | |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint: Change in Hbg | Comparison groups | Danicopan vs Placebo |
| | | LS Mean difference | 24.44 |
| | | 95% CI | 16.90, 31.99 |
| | | P-value | <0.0001 |
| | Secondary: Proportion of patients with Hbg increase ≥ 2 g/dL | Comparison groups | Danicopan vs Placebo |
| | | Difference | 46.9 |
| | | 95% CI | 29.2, 64.7 |
| | | P-value | < 0.0001 |
| | Secondary: transfusion avoidance | Comparison groups | Danicopan vs Placebo |
| | | Difference | 41.7 |
| | | 95% CI | 22.7, 60.8 |
| | | P-value | 0.0004 |
| | Secondary: Change in FACIT-Fatigue score | Comparison groups | Danicopan vs Placebo |
| | | LS Mean difference | 6.12 |
| | | 95% CI | 2.33, 9.91 |
| | | P-value | 0.0021 |
| | Secondary: Change in absolute reticulocyte count | Comparison groups | Danicopan vs Placebo |
| | | LS Mean difference | -87.2 |
| | | 95% CI | -117.7, -56.7 |
| | | P-value | <0.0001 |

| Title: A Phase 3 Study of danicopan (ALXN2040) as add-on therapy to a C5 Inhibitor (eculizumab or ravulizumab) in patients with paroxysmal nocturnal haemoglobinuria who have clinically evident extravascular haemolysis (EVH) | |
|---|---|
| Study identifier | ALXN2040-PNH-301; 2019-003829-18; NCT04469465 |
| Notes | |

### *2.6.5.3. Clinical studies in special populations*

**Table 74: Clinical studies in special populations**

| | Age 65-74 (Older subjects number/total number) | Age 75-84 (Older subjects number/total number) | Age 85+ (Older subjects number/total number) |
|---|---|---|---|
| Controlled trials[a] | 11/73 | 9/73 | 0/73 |
| Non controlled trials[b] | 2/22 | 0/22 | 0/22 |

[a] Data from Study ALXN2040-PNH-301 (Interim Safety Analysis Set)
[b] Data from Studies ACH471-101, ACH471-100, and ACH471-103

### *2.6.5.4. In vitro biomarker test for patient selection for efficacy*

Not applicable

### *2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)*

Not applicable

### *2.6.5.6. Supportive study(ies)*

**Study ACH471-101**

Study ACH471-101 is an ongoing multicentre, open-label, multiple-dose Phase 2 study to evaluate the efficacy of danicopan as an add-on treatment to eculizumab therapy in adult participants with PNH who had inadequate response to eculizumab treatment.

The study consisted of a **24-Week Treatment Period** and an **LTE Period**. During the 24-Week Treatment Period, participants received daily oral treatment with danicopan as add-on treatment to intravenous (IV) eculizumab administered at the participant's usual dose and schedule. Four groups of participants were planned to be enrolled sequentially based on planned danicopan starting doses of 100 mg tid, 150 mg tid, 200 mg tid, and an optimal dose as determined from data from the first 3 groups. Each dose level had to remain at that dose level for a minimum of 4 weeks before dosing of the subsequent group of participants at the next highest dose levels. Danicopan dose could then be increased for each participant, to 200 mg tid based on safety and Hgb values at protocol-specified timepoints, after a minimum of 4 weeks of treatment at the lower dose level during the 24-Week Treatment Period.

After completion of the 24-Week Treatment Period, participants could continue into the LTE and receive the same dose of danicopan plus eculizumab treatment they received at the end of the 24-Week Treatment Period, or if clinically indicated, could dose escalate up to 200 mg tid. Participants

were allowed to switch from eculizumab to ravulizumab during the LTE Period. During the LTE Period, participants returned to the clinic every 8 weeks, with a local laboratory visit 4 weeks after every clinic visit starting at Week 28.

Study participants

Adult patients with PNH and with **RBC transfusion-dependent anaemia** (defined as having received at least at least one RBC transfusion within 12 weeks prior to Screening) who are receiving a stable dose of eculizumab (have been receiving eculizumab at approved or higher doses for at least 24 weeks prior to entry and without change in dose or schedule for at least 8 weeks) and who had inadequate response to eculizumab monotherapy were enrolled in this study.

Treatment

Danicopan was dosed orally over a 24-Week period while participants continued to receive eculizumab at their usual dose and schedule. Planned and administered starting doses of danicopan were as follows:

| | Planned starting dose | Administered starting dose |
|---|---|---|
| Group 1 | 100 mg tid | 100 mg tid |
| Group 2 | 150 mg tid | 150 mg tid |
| Group 3 | 200 mg tid | 100 mg tid |
| Group 4 | Optimal dose | 100 mg tid |

Dose escalations to the next highest dose up to a maximum dose of 200 mg tid were allowed on an individual basis at the discretion of the Investigator in consultation with the Sponsor. At the end of treatment, participants who did not transition to another study were to complete a 6-day Taper of danicopan while continuing eculizumab treatment at their usual dose and schedule.

**Table 75: Study ACH471-101 Efficacy Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the efficacy of danicopan plus eculizumab based on the increase in Hgb relative to Baseline during 24 weeks of treatment | • Change in Hgb level from Baseline at Week 24 |
| **Secondary** | |
| • To evaluate the efficacy of danicopan plus eculizumab based on the reduction in the number of RBC units transfused during the 24 weeks of treatment with danicopan compared to the 24 weeks prior to initiation of treatment with danicopan | • Reduction in the number of RBC units transfused and transfusion instances during the 24 weeks of treatment with danicopan compared to the 24 weeks prior to initiation of treatment with danicopan |
| • To evaluate the efficacy of danicopan plus eculizumab based on the percentage of participants who are RBC transfusion independent during 24 weeks of treatment | • Number and proportion of participants who are RBC transfusion independent at 24 weeks of treatment |
| • To evaluate the efficacy of danicopan plus eculizumab based on the change from Baseline in LDH during 24 weeks of treatment | • Change in LDH level from Baseline at Week 24 |
| **Exploratory**[a] | |
| • To evaluate health-related quality-of-life measures during 24 weeks of treatment | • Total score and change from Baseline on the FACIT-Fatigue scale instrument at scheduled timepoints |

[a] Other prespecified exploratory objectives and endpoints not described in this Summary of Clinical Efficacy are included in ACH471-101 Interim CSR.

Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; Hgb = hemoglobin; LDH = lactate dehydrogenase; RBC = red blood cell

**Results**

Of the 12 enrolled participants, 11 participants completed 24 weeks of danicopan treatment in the Primary Evaluation Period and are being treated in the LTE part of the study. One participant discontinued on Day 2 due to an unrelated serious treatment-emergent adverse event (TEAE) of pulmonary oedema.

**Outcomes and estimation**

- ***Primary efficacy endpoint***

The primary endpoint was change from baseline in Hgb level at Week 24. Mean (SD) Hgb levels increased from baseline (79.4 [14.25] g/L) at Week 24 (103.3 [16.61] g/L) by 23.9 (13.33) g/L.

Hgb levels started increasing by Week 1. Mean (SD) change from Baseline at Week 2 was 20.5 (7.10) g/L, indicating an early efficacy effect.

**Table 76: Summary of Haemoglobin and Change from Baseline at Week 1, Week 2, and Week 24 – mITT Population Set**

| Visit<br>Statistic | All Participants N = 11 | | |
|---|---|---|---|
| | Baseline | Observed | Change from Baseline |
| **Hemoglobin (g/L)** | | | |
| **Baseline** | | | |
| n | NA | 11 | NA |
| Mean (SD) | NA | 79.4 (14.25) | NA |
| Median | NA | 77.0 | NA |
| Min, max | NA | 50, 104 | NA |

| Visit<br>Statistic | All Participants N = 11 | | |
|---|---|---|---|
| | Baseline | Observed | Change from Baseline |
| **Week 1** | | | |
| n | | 11 | |
| Mean (SD) | 79.4 (14.25) | 95.1 (14.48) | 15.7 (7.38) |
| Median | 77.0 | 96.0 | 14.0 |
| Min, max | 50, 104 | 61, 112 | 6, 27 |
| **Week 2** | | | |
| n | | 11 | |
| Mean (SD) | 79.4 (14.25) | 99.9 (12.61) | 20.5 (7.10) |
| Median | 77.0 | 102.0 | 20.0 |
| Min, max | 50, 104 | 70, 116 | 9, 32 |
| **Week 24** | | | |
| n | | 11 | |
| Mean (SD) | 79.4 (14.25) | 103.3 (16.61) | 23.9 (13.33) |
| Median | 77.0 | 106.0 | 31.0 |
| Min, max | 50, 104 | 75, 133 | -2, 38 |

Note: Change was summarized only for participants who had data at both Baseline and Week 24. Baseline was defined as the last nonmissing value prior to the first dose of danicopan.
Abbreviations: max = maximum; min = minimum; mITT = modified intent-to-treat; NA = not applicable; SD = standard deviation

***Secondary efficacy endpoints***

- Red Blood Cell Transfusions

A reduction of transfusion burden, indicated by reduced transfusion instances and reduced number of units transfused was observed. During the 24-Week Treatment Period, mean (± SD) reduction in the number of RBC units transfused was 4.4 (± 4.13) and mean reduction in the number of transfusion instances was 2.7 (± 2.45) for the 11 participants in the mITT Population.

In the 24 weeks prior to initiation of danicopan, 50 units of RBCs were transfused in 31 transfusion instances to 10 participants compared with only 2 RBC units transfused to 1 participant in 1 instance during the 24-Week Treatment Period.

**Table 77: Summary of Red Blood Cell Transfusions from Baseline at Week 24 – mITT Population Set**

| | All Participants N = 11 |
|---|---|
| Participants without RBC transfusions 24 weeks prior to the initiation of danicopan, n (%) | 1 (9.1) |
| Participants without RBC transfusions during the 24-Week Treatment Period, n (%) | 10 (90.9) |
| Number of RBC units transfused during the 24-Week Treatment Period | |
| n | 11 |
| Mean (SD) | 0.2 (0.60) |
| Median (IQR) | 0 |
| Min, max | 0, 2 |
| Reduction in the number of RBC units transfused | |
| n | 11 |
| Mean (SD) | 4.4 (4.13) |
| Median (IQR) | 3.0 (7.0) |
| Min, max | 0, 11 |
| Number of RBC transfusion instances during the 24-Week Treatment Period | |
| n | 11 |
| Mean (SD) | 0.1 (0.30) |
| Median (IQR) | 0.0 (0.0) |
| Min, max | 0, 1 |
| Reduction in the number of RBC transfusion instances | |
| n | 11 |
| Mean (SD) | 2.7 (2.45) |
| Median (IQR) | 2.0 (4.0) |
| Min, max | 0, 8 |

Note: Number of RBC transfusion instances and number of RBC units transfused are 0 for calculating summary statistics for participants without any RBC transfusion. Reduction in the number of RBC transfusion instances and RBC units transfused are calculated as the difference between the 24-Week Treatment Period and the 24 weeks prior to the initiation of danicopan.

Abbreviations: IQR = interquartile range; max = maximum; min = minimum; mITT = modified intent-to-treat; RBC = red blood cell; SD = standard deviation

In the 24 weeks prior to initiation of danicopan, 10 (90.9%) of 11 participants had RBC transfusions. During the 24-Week Treatment Period, 10 (90.9%) participants were RBC transfusion-free. Results were similar in the Sensitivity Analysis Population Set which excluded one participant who did not receive blood transfusions for religious reasons.

The participant who received the transfusion during the 24-Week Treatment Period had a Hgb value of 6.8 g/L and platelet count of 177 × $10^9$/L and was given 2 units of pRBCs for anaemia on Day 149.

- *Lactate dehydrogenase*

The LDH level mean (± SD) remained stable from baseline (244.5 [± 74.40] U/L) to Week 24 (239.5 [± 48.48] U/L).

**Table 78: Summary of Lactate Dehydrogenase and Change from Baseline at Week 24 – mITT Population Set**

| Visit<br>Statistic | All Participants<br>N = 11 |
|---|---|
| **Lactate Dehydrogenase (U/L)** | |
| **Baseline** | |
| n | 11 |
| Mean (SD) | 244.5 (74.40) |
| Median | 226.0 |
| Min, max | 146, 378 |
| **Week 24** | |
| n | 11 |
| Mean (SD) | 239.5 (48.48) |
| Median | 228.0 |
| Min, max | 184, 343 |
| **Change from baseline** | |
| n | 11 |
| Mean (SD) | -5.0 (48.60) |
| Median | -15.0 |
| Min, max | -110, 83 |

Note: Change was summarized only for participants who had data at both Baseline and Week 24. Baseline was defined as the last nonmissing value prior to the first dose of danicopan.
Abbreviations: max = maximum; min = minimum; mITT = modified intent-to-treat; SD = standard deviation

## 2.6.6. Discussion on clinical efficacy

The main evidence in support of this application is the Phase 3 study ALXN2040-PNH-301. Moreover, results of an open-label Phase 2 study (ACH471-101) of danicopan as add-on treatment to eculizumab have been provided as supportive. In addition, two proof-of-concept open label studies evaluating danicopan as monotherapy were presented (study ACH471-100, with extension in study ACH471-103).

Dose-response study

The selected dose used in study ALX2040-PNH-301 was based on safety data from different studies with danicopan in PNH (ACH471-101, ACH471-100, and ACH471-103) and complement 3 glomerulopathy (C3G)/ immune-complex membranoproliferative glomerulonephritis [IC-MPGN] (ACH471-201, ACH471-204, and ACH471-205) along with the efficacy data observed in study ACH471-101 and PK/PD modeling and simulation.

***Design and conduct of clinical studies***

The **study ALXN2040-PNH-301** is a randomised, double-blind, placebo-controlled Phase 3 study in patients with PNH and clinically significant evidence of extravascular haemolysis while on treatment with a C5 inhibitor.

The study consisted of two treatment periods, one randomised treatment period up to Week 12 (TP1) in which patients were randomised to receive either danicopan or placebo, in addition to their background therapy with eculizumab or ravulizumab, and an open-label treatment period up to Week 24 (TP2) in which patients receiving placebo in TP1 switched to receive danicopan while patients receiving danicopan continue to receive it. Patients who completed TP2 may enter the Long-Term Extension Period, up to a maximum of 2 years.

The eligibility criteria allowed the inclusion of adult patients with PNH that had been receiving an approved C5 inhibitor (i.e. eculizumab or ravulizumab) for at least 6 months with no change in the prescribed dose or interval and had clinical evidence of EVH (i.e. Hgb ≤ 9.5 g/dL with absolute reticulocyte count ≥ 120 × $10^9$/L). Patients were included in the study regardless of their requirement for transfusions. Of note, patients on iron, folic acid and/or B12 supplementation were eligible if on stable dose for at least 30 days prior enter the study. All patients should have been vaccinated against meningococcal infection. Overall, the inclusion and exclusion criteria are considered acceptable.

Patients were randomised 2:1 to receive either danicopan or placebo and as already stated, all patients received background therapy with a C5 inhibitor (i.e. eculizumab or ravulizumab). Randomisation was stratified by transfusion history (> 2 or ≤ 2 transfusions within 6 months of screening), Hgb (< 8.5 g/dL vs. ≥ 8.5 g/dL) at screening, and being Japanese/non-Japanese.

The initial dose of danicopan was 150 mg tid but this dose could be escalated to a maximum of 200 mg tid at protocol-specified timepoints based on safety and clinical assessment, either during the treatment periods or the LTE. Of note, if a patient requires treatment discontinuation, tapering of danicopan over 6 days was required due to the possibility of ALT elevations.

The primary endpoint of the study was change in Hgb from baseline to week 12. This was considered acceptable during the SA (MA/CHMP/SAWP/26111/2020). Transfusion avoidance (TA) is considered a relevant objective of treatment and, in fact, it was suggested to be included as a co-primary endpoint during the kick-off meeting held on 22nd April 2020, though this recommendation was not followed. TA has been included as key secondary endpoint. Key secondary endpoints were proportion of patients with Hgb increase of ≥2 g/dL in the absence of transfusions, proportion of patients with TA, change from baseline in FACIT-Fatigue scores and change from baseline in absolute reticulocyte count (ARC), all assessed at week 12.

Of note, breakthrough haemolysis (BTH) has not been studied as efficacy endpoint within the danicopan clinical studies. Since PNH clone size increases due to the inhibition of factor D, missed danicopan doses or treatment discontinuation without appropriate tapering might result in BTH, sometimes a catastrophic one. BTH and haemolysis have been presented as adverse event (see safety section).

Sample size and statistical methods

Approximately 84 patients were planned to be enrolled in the study, with the assumption of approximately 10% of drop-out. For the primary endpoint the statistical power using 2-sample t-test would be 99% to detect the difference in mean change from baseline of 2 g/dL (alternative hypothesis), assuming the 2-sided statistical significance level of 0.05 and the SD of 1.6 g/dL, which according to the Applicant was estimated from results of Study ACH471-101. Overall, the assumptions

and calculations used for estimating the sample size (accounting also for a possible 10% drop-out rate) are acceptable.

The primary endpoint has been analysed using MMRM which includes the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the continuous fixed covariate of baseline haemoglobin value and the stratification randomisation indicator of transfusion history in the model. Several sensitivity analysis were also planned, including a tipping point analysis by assessing the treatment effect under alternative missing data assumptions. The method to analyse the primary endpoint is considered adequate as well as the sensitivity analyses although a placebo imputation or baseline observation carried forward method might have been included as sensitivity analysis.

A number of secondary efficacy endpoints have been analysed using a hierarchical fixed sequence test procedure to determine the statistical significance at a two-sided level of 0.05 for each endpoint sequentially. The sequential testing strategy to control for a possible inflation of the type I error in the pre-specified set of secondary endpoints is adequate from a statistical perspective.

Of note, an interim analysis was pre-planned when approximately 75% of patients have been randomly assigned to study treatment and have had the opportunity to complete the 12-week TP1 (information fraction = 0.75). The gamma family alpha-spending function with parameter -4 is used to control for multiplicity at the interim analysis. Specifically, the alpha level assigned for the primary endpoint at interim is 2-sided 0.018. From a methodological perspective, the timing of the interim analysis and the strategy to control the inflation of the type I error due to multiple looks at the data is agreed and no concerns are raised.

***Efficacy data and additional analyses***

A total of 105 patients were screened, of whom 23 patients were screen failure. Besides, 9 patients were in screening at the time of the data cut-off. The main reason for screening failure were not meeting inclusion/exclusion criteria (n=19), mainly inclusion criterion 2 (i.e. clinically evident EVH). There were also 4 patients that were excluded due to "other" reasons.

Results provided as part of the initial submission were based on the first interim analysis (IA) with a data cut-off date (DCO) of 28 Jun 2022. As part of the responses to the D120 list of questions updated efficacy data were submitted, including results of two additional IA. As of the DCO for the IA3 (31 Mar 2023) 86 patients were randomised. Of these, 82 completed TP1 and entered TP2 and 80 patients completed TP2 and entered LTE period. As of the DCO, 58 patients were ongoing in the LTE and 32 patients had completed 1 year.

<u>Protocol amendments</u>

The original protocol (dated 18 Nov 2019) has suffered 6 global amendments. The most significant modifications can be found in the first protocol amendment (dated 17 Apr 2020), where the study was changed to a double-blind design, the sample size was increased and an interim analysis was added (among other adjustments). However, as the first patient was enrolled on 06 Jan 2021, this amendment does not entail significant methodological issues.

Of note, with Amendment 5 (dated 16 Jul 2021), the planned IA was modified to be performed when 75% of patients have been randomly assigned rather than 50%, as initially planned. This is welcome. Moreover, with Amendment 6 (dated 25 Feb 2022), a new (key) secondary endpoint was added, and the transfusion requirement prior to start of study was removed (the proposed cap up to 40% of the enrolment of patients with < 2 transfusions was removed).

Further, in Amendment 6.3 (dated 08 Aug 2022), only applicable to the US, the Applicant updated the test used for the analysis of the primary efficacy endpoint to compare the difference in Hgb change from baseline to Week 12 between treatment groups. This was done using a rerandomisation test at a two-sided 0.05 significance level, thus relegating the original primary analysis (i.e. MMRM) to a sensitivity analysis. In the non-US countries, MMRM remained as the primary analysis while the rerandomisation test was included as sensitivity analysis. This change is not expected to have an impact in the interpretation of the outcome of the study; moreover, results based on these two different analyses were consistent.

Baseline characteristics

In the all randomised patients, the median age was of 54 (range: 20, 82) years. There were only 9 (10.5%) patients ≥ 75 years. 63% of patients were female, 49% white and 37% Asian. Of note, the proportion of male patients was higher in the danicopan arm.

All patients enrolled were on stable C5 inhibitor therapy. The median duration from initial and current C5 inhibitor to first dose of study treatment was, respectively, 4.35 years and 3.5 years. Regarding current C5 inhibitor, 51 (59.3%) patients were receiving ravulizumab while 35 (40.7%) were receiving eculizumab.

Mean Hgb at baseline was 7.75 (range: 5.4, 9.4) g/dL, being Hgb level <8.5 g/dL in 52 (60.5%) patients. Absolute reticulocyte count (ARC) at baseline (median) was 211.30x $10^9$/ L.

Concerning transfusion requirements, all patients had received transfusions during the 6 months prior to screening; 50 (58%) received ≤ 2 transfusions. Of these, 76 (88.4%) and 60 (69.8), respectively, received transfusions within 24 and 12 weeks prior to receiving study treatment. The median number of transfusions within 24 weeks prior to study treatment initiation was of 2 (range: 0, 8). Of note, in the original protocol, the proportion of patients with <2 transfusions in the prior 6 months was capped to 40%. However, this requirement was removed with protocol amendment 6, as stated above.

The initial starting dose of danicopan was 150 mg tid but it could be escalated up to 200 mg tid. During the TP1, 3 patients initiated danicopan at a dose of 100 mg tid (this option was removed with protocol amendment 4.0) and 54 at a dose of 150 mg tid; of these, 14 patients escalated to 200 mg tid during TP1. Up to the DCO, of the 84 patients exposed to danicopan, 59 were dose escalated to 200 mg tid. Data on Hgb prior to dose escalation and after dose escalation up to 12 weeks have been provided. Mean Hgb prior to dose escalation in these 59 patients was 10.2 g/dL. Two weeks after dose-escalation mean Hgb was 10.7 g/dL and was maintained over time. Among patients with an increase in the dose of danicopan, with laboratory results available and no transfusions during the preceding four weeks (n=45), 19 patients had an Hgb increase ≥0.5 g/dL and 8 patients ≥1 g/dL, 2 weeks after the dose escalation.

Outcomes and estimation

All the efficacy analyses initially provided were based on the interim efficacy analysis set which is comprised by 63 patients (42 danicopan arm and 21 placebo arm). Results of a third IA were provided during the procedure. This IA3 was based on the modified randomised population comprised by 83 patients (three patients were excluded due to early switching to danicopan before completing TP1).

At the time of the IA1 (interim efficacy analysis set) the study met its **primary endpoint**. The LS mean (SE) change from baseline in Hgb at week 12 using MMRM was 29.40 (2.107) g/L in the danicopan group compared with 4.96 (3.128) g/L in the placebo group. The LS mean difference (SE) between the two groups was 2.44 g/dL; p<0.0001. The re-randomisation test analysis showed statistically significant results (p = 0.0007). An increase of 2 g/dL (20 g/L) can be considered of clinical relevance. Sensitivity analyses were consistent with the primary analysis.

The results in the **key secondary endpoints** supported the primary analysis. Statistically significant differences were observed between treatment arms in the proportion of patients with Hgb increase of ≥ 20 g/L in the absence of transfusion at week 12 (46.9%; 95% CI: 29.16, 64.68; p-value<0.0001), and in the proportion of patients that achieved transfusion avoidance (41.7%; 95% CI: 22.67, 60.77; p-value=0.0004).

The mean absolute reticulocyte count (ARC) at baseline was 236.37 x $10^9$/L in the danicopan arm and 240.64 x $10^9$/L in the placebo arm. At week 12 the LS mean difference between treatment arms was -87.2 x $10^9$/L (95% CI -117.7, -56.7), p-value<0.0001.

The change from baseline to week 12 in FACIT-fatigue score was a (key) secondary endpoint in the study. The FACIT-Fatigue questionnaire consists of 13 items scored on a 5-point Likert scale (0=not at all, 4=very much). The score has a range of 0 through 52 with higher score being indicative of a better quality of life (QoL). The mean FACIT-fatigue scores at baseline were comparable between treatment arms (33.46 danicopan vs. 33.86 placebo). The LS mean change form baseline at week 12 was 7.97 in the danicopan arm and 1.85 in the placebo arm, with a difference between treatment arms of 6.12 (95% CI: 2.33, 9.91); p-value = 0.0021.

At **IA3** (modified randomised set) results were overall consistent with the results of the IA1. Mean change in haemoglobin level (g/dL) from baseline to week 12 was 2.40 (95% CI: 1.68, 3.13), treatment difference in the proportion of patients with Hgb increase≥2 g/dL was of 46.9 (95% CI: 31.5, 62.4) and the treatment difference in the change in ARC ($10^9$/L) was of -89.6 (95% CI: -118.5, -60.8). Change in FACIT-Fatigue score was slightly lower, with a treatment difference of 5.71 (95% CI: 2.56, 8.86), although within the threshold for clinical significance (i.e. ≥5 points). Results from the primary and key secondary endpoints for the all randomised patients population (n=86) submitted were consistent with those of the modified randomised set.

Subgroup analyses for the primary and key secondary endpoints were submitted. Overall, results appear consistent between the subgroups analysed.

Statistically significant differences in favour of danicopan were also observed in **other secondary endpoints**, such as the number of RBC units transfused and transfusion instances and change in total bilirubin and direct bilirubin.

Patients treated with danicopan experienced an increase in PNH clone size compared with those that received placebo, with a LS mean change of 24.60 in the danicopan arm versus -3.04 in the placebo arm (difference between treatment arms of 27.63; 95% CI: 13.03, 42.24) at IA1. This appears to be related with the mechanism of action of danicopan. A reduction in C3 fragment deposition on PNH RBCs was also observed with a LS mean change of -15.41 in the danicopan arm and 0.79 in the placebo arm (difference -16.20; 95% CI: -26.91, -5.48). Similar results were observed at IA3.

A higher number of patients in the danicopan group compared with the placebo group presented Hgb normalisation (28.6% vs. 0, respectively), with a difference of 18.4 (95% CI: -0.84, 37.71) at IA1. Similar results were observed at IA3.

During **TP2** (i.e. 24 weeks) patients who were receiving placebo switched to danicopan while those already receiving danicopan during TP1 continued with danicopan. Overall, at IA3, the efficacy observed in the danicopan group during TP1 was maintained during TP2 while in the placebo arm, an improvement in most of the endpoints was observed during TP2 after switching to danicopan. Of note, the proportion of patients with Hgb increase ≥2 g/dL in the absence of transfusion was lower during TP2 (41.8% [95% CI: 28.65, 55.89]) compared with TP1 (54.4%; 95% CI: 40.66, 67.64).

After completion TP2 patients continued **LTE period** up to 2 years. Up to the data cut-off for IA3, 80 patients had entered LTE and 32 patients had completed 1 year. The efficacy was maintained over

time, although data in the long term are still considered limited. The Applicant has committed to providing the final CSR of study ALXN2040-PNH-301, which is expected by Q1 2026 (REC).

Justification as an add-on therapy

The aim of a satisfactory treatment should be to control both intravascular haemolysis (IVH) and extravascular haemolysis (EVH). The approved C5 inhibitors eculizumab and ravulizumab, have increased survival and improved outcomes in PNH by controlling IVH, reflected in LDH improvements. However, these products do not specifically control EVH and in many patients treated with C5 inhibitors although LDH is largely controlled, ARC and bilirubin levels remain elevated, indicating ongoing haemolysis. This often translates into remaining symptomatology and some patients still require RBC transfusions. Evidence currently available suggests that the use of danicopan in monotherapy is not providing adequate control of the most relevant features of PNH, i.e. control of IVH. In this context, the rationale for the combination of danicopan as add-on to eculizumab or ravulizumab to address EVH while eculizumab and ravulizumab maintain control of IVH is acknowledged.

The finally agreed wording of the indication is as follows:

*Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia (see section 5.1).*

## 2.6.7. Conclusions on the clinical efficacy

In the study ALXN2040-PNH-301, the addition of danicopan to background therapy with a C5 inhibitor (ravulizumab or eculizumab) demonstrated an improvement in the mean change in Hgb from baseline to week 12 compared with ravulizumab or eculizumab as monotherapy. Improvements were also observed in the secondary endpoints.

To further characterise the long-term efficacy (and safety) of danicopan as add-on to ravulizumab or eculizumab in PNH patients, the final CSR of study ALXN2040-PNH-301 should be submitted (REC).

## 2.6.8. Clinical safety

The safety profile of danicopan (ALXN2040) orally administered complement factor D inhibitor as an add-on to ravulizumab or eculizumab for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) is based on the following clinical studies:

- Study ALXN2040-PNH-301, pivotal Phase 3, randomized, double-blind, placebo-controlled study in participants with PNH who have clinically significant EVH while on treatment with ravulizumab or eculizumab (n=57 danicopan arm, n=29 placebo arm, data cutoff 31 Mar 2023, (IA3)). During Treatment Period 1 (TP1), the safety profile of add-on danicopan group was directly compared with that of the parallel add-on placebo group, both administered as add-on treatment to ravulizumab or eculizumab. The treatment allocation was assigned randomly and remained blinded until the time of interim analysis.

Pooled safety data from all participants exposed at similar danicopan dose regimen from Phase 2 and Phase 3 studies:

- *PNH Add-on Population* comprised Study ALXN2040-PNH-301 (IA3 data cutoff 31 Mar 2023) and Study ACH471-101 (IA data cutoff date 31 Mar 2023, N=12) who received danicopan as an add-on therapy to ravulizumab or eculizumab as background C5 inhibitors for PNH

treatment: a total of 96 patients exposed to danicopan as add-on to C5i with a median treatment duration of 452,5 days.

- *PNH Monotherapy Population* comprised 2 completed Phase 2 studies: Study ACH471-100 and Study ACH471-103 which includes all participants who received only danicopan for PNH treatment: 10 patients exposed to danicopan monotherapy with a median treatment duration of 841.5 days.
- *All PNH Population* combined the Add-on and Monotherapy Populations, which includes all participants in Studies ACH471-100, ACH471-101, ACH471-103, and ALXN2040-PNH-301 who received at least 1 dose of danicopan.
- *C3G/IC-MPGN Population* comprised 3 completed Phase 2 studies where patients were exposed at similar doses as PNH add-on and monotherapy population. These include all participants in Studies ACH471-201, ACH471-204, and ACH471-205 who received at least 1 dose of danicopan: 37 patients exposed to danicopan with a median treatment duration of 502 days. These studies provide additional data supporting the safety of long-term treatment with danicopan at similar doses as those investigated in the PNH development programme.
- *Combined PNH and C3G/IC-MPGN Population* which represents the pooling of all participants with PNH and all participants with C3G/IC-MPGN who were treated with danicopan. Comprised the All PNH and C3G/IC-MPGN Populations.

#### *2.6.8.1. Patient exposure*

In total, 799 subjects were exposed to danicopan: 106 with PNH, 37 with C3G/IC-MPGN, 273 with GA, 367 healthy participants, 8 healthy participants with renal impairment and 8 healthy participants with hepatic impairment at the data cutoff of the initial submission (data cutoff 31 Mar 2023).

Phase 3 PNH Study ALXN2040-PNH-301:

Median exposure duration to danicopan by dose level (100 mg, 150 mg, and 200 mg dose levels) is summarized in Table 79 (data cutoff 31 Mar 2023).

**Table 79: Study ALXN2040-PNH-301. Study Intervention Exposure –Interim Analysis 3 (31 Mar 2023)**

| | TP1 | | TP2 | | | LTE | | | Entire Study | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | DAN N = 57 | PBO N = 29 | DAN/DAN[a] N = 55 | PBO/DAN[b] N = 27 | Total N = 82 | DAN/DAN[a] N = 54 | PBO/DAN[b] N = 26 | Total N = 80 | DAN/DAN[a] N = 57 | PBO/DAN[b] N = 27 | Total[c] N = 84 |
| **Treatment duration (days)** | | | | | | | | | | | |
| n | 57 | 29 | 55 | 27 | 82 | 54 | 26 | 80 | 57 | 27 | 84 |
| Mean (SD) | 82.8 (7.15) | 77.3 (15.71) | 82.8 (9.44) | 83.5 (2.55) | 83.0 (7.85) | 293.9 (156.26) | 321.4 (171.00) | 302.9 (160.63) | 441.9 (176.02) | 393.7 (178.96) | 426.4 (177.34) |
| Median | 84.0 | 84.0 | 84.0 | 84.0 | 84.0 | 284.5 | 310.5 | 288.5 | 439.0 | 381.0 | 427.5 |
| Min, max | 44.0, 88.0 | 35.0, 86.0 | 15.0, 94.0 | 71.0, 85.0 | 15.0, 94.0 | 46.0, 601.0 | 15.0, 611.0 | 15.0, 611.0 | 44.0, 769.0 | 77.0, 695.0 | 44.0, 769.0 |
| **Treatment duration (days) by dose level** | | | | | | | | | | | |
| **100 mg** | | | | | | | | | | | |
| n | 3 | NA | 1 | 0 | 1 | 0 | 0 | 0 | 3 | 0 | 3 |
| Mean (SD) | 56.0 (37.04) | NA | 28.0 (NA) | NA | 28.0 (NA) | NA | NA | NA | 65.3 (49.17) | NA | 65.3 (49.17) |
| Median | 70.0 | NA | 28.0 | NA | 28.0 | NA | NA | NA | 70.0 | NA | 70.0 |
| Min, max | 14.0, 84.0 | NA | 28.0, 28.0 | NA | 28.0, 28.0 | NA | NA | NA | 14.0, 112.0 | NA | 14.0, 112.0 |
| **150 mg** | | | | | | | | | | | |
| n | 56 | NA | 24 | 27 | 51 | 16 | 13 | 29 | 57 | 27 | 84 |
| Mean (SD) | 71.6 (19.79) | NA | 68.9 (21.81) | 60.6 (21.27) | 64.5 (21.72) | 206.9 (141.30) | 243.8 (183.92) | 223.4 (159.82) | 157.4 (155.88) | 178.0 (192.78) | 164.0 (167.72) |
| Median | 84.0 | NA | 84.0 | 43.0 | 83.0 | 194.0 | 235.0 | 225.0 | 84.0 | 43.0 | 84.0 |
| Min, max | 14.0, 87.0 | NA | 15.0, 94.0 | 41.0, 85.0 | 15.0, 94.0 | 29.0, 501.0 | 4.0, 574.0 | 4.0, 574.0 | 40.0, 669.0 | 41.0, 658.0 | 40.0, 669.0 |
| **200 mg** | | | | | | | | | | | |
| n | 14 | NA | 38 | 15 | 53 | 41 | 15 | 56 | 43 | 16 | 59 |
| Mean (SD) | 39.3 (10.17) | NA | 75.3 (17.89) | 41.3 (3.41) | 65.7 (21.70) | 306.4 (156.11) | 345.8 (172.21) | 317.0 (159.95) | 371.5 (158.51) | 362.9 (190.05) | 369.2 (165.98) |
| Median | 42.0 | NA | 84.0 | 42.0 | 83.0 | 300.0 | 368.0 | 313.5 | 365.0 | 393.5 | 369.0 |
| Min, max | 7.0, 48.0 | NA | 27.0, 85.0 | 29.0, 43.0 | 27.0, 85.0 | 46.0, 601.0 | 11.0, 611.0 | 11.0, 611.0 | 7.0, 666.0 | 30.0, 654.0 | 7.0, 666.0 |

Note: Treatment duration is derived as date of last dose - date of first dose + 1 day.

[a] Participants received danicopan in TP1 and continued with danicopan during TP2 and LTE.

[b] Participants received placebo in TP1, switched to danicopan during TP2, and continued receiving danicopan during LTE.

[c] Exposure duration is for danicopan exposure only and does not include placebo exposure, which is covered in the TP1 column.

Abbreviations: DAN = danicopan; LTE = long-term extension; max = maximum; min = minimum; N = number of participants; n = number of participants in each category; NA = not applicable; SD = standard deviation

In the safety data cutoff 31 Mar 2023 (IA3), all participants completed TP1 (57 participants received danicopan, and 29 participants received placebo) and entered TP2 (n = 82), with the exception of 4 participants who discontinued during TP1 (2 in the danicopan group and 2 in the placebo group).

Overall, 84 participants have been exposed to danicopan (2 participants randomized to placebo discontinued during TP1 and were not exposed to danicopan). The median (range) duration of treatment during TP1 was 84.0 (44.0 to 88.0) days for add on danicopan group (n = 57) and 84.0 (35.0 to 86.0) days for the add-on placebo group (N = 29). In the danicopan treatment group, 3 participants received 100 mg danicopan for a median (range) duration of 70.0 (14.0 to 84.0) days. The 150-mg dose was received by 56 participants for a median (range) duration of 84.0 (14.0 to 87.0) days, and the 200-mg dose was received by 14 participants for a median (range) duration of 42.0 (7.0 to 48.0) days. The overall median (range) exposure to danicopan during the entire study through the data cutoff is 427.5 (44.0 to 769.0) days.

Pooled Studies

The treatment duration in pooled studies is summarized in Table 80 (data cutoff 31 Mar 2023)

**Table 80: Treatment Duration (Combined PNH and C3G/IC-MPGN Population)**

| Variable | PNH Add-on (N = 96) | PNH Monotherapy (N = 10) | All PNH (N = 106) | C3G/ IC-MPGN (N = 37) | Combined PNH and C3G/ IC-MPGN (N = 143) |
|---|---|---|---|---|---|
| **Treatment duration (days)** | | | | | |
| n | 96 | 10 | 106 | 37 | 143 |
| Mean (SD) | 538.3 (372.86) | 799.2 (491.86) | 562.9 (390.38) | 477.4 (237.09) | 540.8 (358.26) |
| Median | 452.5 | 841.5 | 469.0 | 502.0 | 491.0 |
| Min, max | 1, 1631 | 41, 1438 | 1, 1631 | 21, 843 | 1, 1631 |
| **Treatment duration category, n (%)** | | | | | |
| 1 day – 12 weeks | 4 (4.2) | 2 (20.0) | 6 (5.7) | 5 (13.5) | 11 (7.7) |
| > 12 – 24 weeks | 2 (2.1) | 0 | 2 (1.9) | 0 | 2 (1.4) |
| > 24 – 48 weeks | 24 (25.0) | 0 | 24 (22.6) | 3 (8.1) | 27 (18.9) |
| > 48 – 72 weeks | 25 (26.0) | 1 (10.0) | 26 (24.5) | 11 (29.7) | 37 (25.9) |
| > 72 – 96 weeks | 22 (22.9) | 0 | 22 (20.8) | 10 (27.0) | 32 (22.4) |
| > 96 – 120 weeks | 8 (8.3) | 2 (20.0) | 10 (9.4) | 7 (18.9) | 17 (11.9) |
| > 120 – 144 weeks | 0 | 2 (20.0) | 2 (1.9) | 1 (2.7) | 3 (2.1) |
| > 144 – 168 weeks | 0 | 0 | 0 | 0 | 0 |
| > 168 – 192 weeks | 3 (3.1) | 2 (20.0) | 5 (4.7) | 0 | 5 (3.5) |
| > 192 weeks | 8 (8.3) | 1 (10.0) | 9 (8.5) | 0 | 9 (6.3) |
| **Treatment duration category, n (%)** | | | | | |
| ≤ 12 weeks | 4 (4.2) | 2 (20.0) | 6 (5.7) | 5 (13.5) | 11 (7.7) |
| > 12 weeks | 92 (95.8) | 8 (80.0) | 100 (94.3) | 32 (86.5) | 132 (92.3) |
| > 24 weeks | 90 (93.8) | 8 (80.0) | 98 (92.5) | 32 (86.5) | 130 (90.9) |
| > 48 weeks | 66 (68.8) | 8 (80.0) | 74 (69.8) | 29 (78.4) | 103 (72.0) |
| > 72 weeks | 41 (42.7) | 7 (70.0) | 48 (45.3) | 18 (48.6) | 66 (46.2) |
| > 96 weeks | 19 (19.8) | 7 (70.0) | 26 (24.5) | 8 (21.6) | 34 (23.8) |
| > 120 weeks | 11 (11.5) | 5 (50.0) | 16 (15.1) | 1 (2.7) | 17 (11.9) |
| > 144 weeks | 11 (11.5) | 3 (30.0) | 14 (13.2) | 0 | 14 (9.8) |
| > 168 weeks | 11 (11.5) | 3 (30.0) | 14 (13.2) | 0 | 14 (9.8) |
| > 192 weeks | 8 (8.3) | 1 (10.0) | 9 (8.5) | 0 | 9 (6.3) |

Note: Percentages are based on the total number of participants in each column. Treatment duration = last study dose date prior to ,off or discontinuation - first dose date + 1. For participants who were exposed to danicopan in 2 studies, treatment duration is the total of durations in the first and the second studies.

Abbreviations: C3G = complement 3 glomerulopathy; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; max = maximum; min = minimum; N = number of participants; n = number of participants in each category; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation

Source: Data cut 31Mar2023, ISS Table 2.7.4.1.3.3.1

### *2.6.8.2. Adverse events*

Phase 3 PNH Study ALXN2040-PNH-301

Overview of all TEAEs reported in Study ALXN2040-PNH-301 during TP1, TP2 and LTE data cutoff 31 Mar 2023 is summarized in tables below:

**Table 81: Overview of All Treatment-Emergent Adverse Events During Treatment Period 1 (Study ALXN2040-PNH-301, Safety Analysis Set, Data Cutoff Date 31 Mar 2023)**

| | Treatment Period 1 | |
|---|---|---|
| | **Danicopan N = 57** | **Placebo N = 29** |
| | **n (%) E** | **n (%) E** |
| Any AE | 43 (75.4) 141 | 18 (62.1) 77 |
| Any SAE | 3 (5.3) 5 | 2 (6.9) 4 |
| Death | 0 | 0 |
| AE leading to withdrawal of study intervention | 3 (5.3) 5 | 1 (3.4) 1 |
| SAE leading to withdrawal of study intervention | 1 (1.8) 2 | 0 |
| **AE by relationship** | | |
| Related<br>Not related | 12 (21.1) 33<br>38 (66.7) 108 | 8 (27.6) 13<br>18 (62.1) 64 |
| **SAE by relationship** | | |
| Related<br>Not related | 1 (1.8) 2<br>3 (5.3) 3 | 0<br>2 (6.9) 4 |
| **AE by toxicity** | | |
| Grade 1<br>Grade 2<br>Grade 3<br>Grade 4<br>Grade 5 | M34 (59.6) 87<br>24 (42.1) 37<br>10 (17.5) 16<br>1 (1.8) 1<br>0 | 116 (55.2) 47<br>15 (51.7) 26<br>4 (13.8) 4<br>0<br>0 |
| **AE of special interest** | | |
| Meningococcal infections<br>Liver enzyme elevations | 0<br>8 (14.0) 13 | 0<br>3 (10.3) 5 |

Note: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = Fatal. AEs are coded using MedDRA Version 25.1.

Abbreviations: AE = adverse event; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Source: Data cut 31Mar2023,

**Table 82: Overview of Treatment-Emergent Adverse Events for Treatment Period 2 (Data Cutoff Date 31 Mar 2023)**

| | **DAN/DAN N = 55 n (%) E** | **Placebo/DAN N = 27 n (%) E** | **Total N = 82 n (%) E** |
|---|---|---|---|
| Any AE | 40 (72.7) 129 | 18 (66.7) 66 | 58 (70.7) 195 |
| Any SAE | 3 (5.5) 4 | 5 (18.5) 5 | 8 (9.8) 9 |
| Death | 0 | 0 | 0 |
| AE Leading to Withdrawal of Study Drug | 0 | 1 (3.7) 1 | 1 (1.2) 1 |
| SAE Leading to Withdrawal of Study Drug | 0 | 0 | 0 |
| **AE by Relationship** | | | |
| Related | 3 (5.5) 3 | 7 (25.9) 17 | 10 (12.2) 20 |
| Not Related | 39 (70.9) 126 | 17 (63.0) 49 | 56 (68.3) 175 |
| **SAE by Relationship** | | | |
| Related | 0 | 1 (3.7) 1 | 1 (1.2) 1 |
| Not Related | 3 (5.5) 4 | 4 (14.8) 4 | 7 (8.5) 8 |
| **AE by Toxicity** | | | |
| Grade 1 | 33 (60.0) 90 | 14 (51.9) 39 | 47 (57.3) 129 |

| | DAN/DAN<br>N = 55<br>n (%) E | Placebo/DAN<br>N = 27<br>n (%) E | Total<br>N = 82<br>n (%) E |
|---|---|---|---|
| Grade 2 | 17 (30.9) 27 | 10 (37.0) 19 | 27 (32.9) 46 |
| Grade 3 | 8 (14.5) 12 | 6 (22.2) 7 | 14 (17.1) 19 |
| Grade 4 | 0 | 1 (3.7) 1 | 1 (1.2) 1 |
| Grade 5 | 0 | 0 | 0 |
| **AE of Special Interest** | | | |
| Meningococcal Infections | 0 | 0 | 0 |
| Liver Enzyme Elevations | 3 (5.5) 4 | 3 (11.1) 3 | 6 (7.3) 7 |

Note: % = n/N × 100. DAN/DAN: Danicopan at Treatment Period 1 and Danicopan at Treatment Period 2; Placebo/DAN: Placebo at Treatment Period 1 and Danicopan at Treatment Period 2. TEAE that has a starting date occurred during a certain Treatment Period is regarded as TEAE at that Treatment Period. Any TEAEs lasted across treatment periods are only counted once in the treatment period the event started. Grade 1=mild; Grade 2=moderate; Grade 3=severe; Grade 4=life-threatening; Grade 5=Fatal. AEs are coded using MedDRA version 25.1.

Abbreviations: AE = adverse event; DAN = danicopan; E = events; N = number of participants; n = number of participants in each category; SAE = serious adverse event; TEAE= treatment-emergent adverse event

**Table 83: Overview of Treatment-Emergent Adverse Events for Long-Term Extension (Data Cutoff Date 31 Mar 2023)**

| | DAN/DAN<br>N = 54<br>n (%) E | Placebo/DAN<br>N = 26<br>n (%) E | Total<br>N = 80<br>n (%) E |
|---|---|---|---|
| Any AE | 41 (75.9) 143 | 22 (84.6) 165 | 63 (78.8) 308 |
| Any SAE | 5 (9.3) 7 | 6 (23.1) 13 | 11 (13.8) 20 |
| Death | 0 | 0 | 0 |
| AE Leading to Withdrawal of Study Drug | 0 | 1 (3.8) 1 | 1 (1.3) 1 |
| SAE Leading to Withdrawal of Study Drug | 0 | 0 | 0 |
| **AE by Relationship** | | | |
| Related | 2 (3.7) 2 | 4 (15.4) 8 | 6 (7.5) 10 |
| Not Related | 41 (75.9) 141 | 22 (84.6) 157 | 63 (78.8) 298 |
| **SAE by Relationship** | | | |
| Related | 0 | 0 | 0 |
| Not Related | 5 (9.3) 7 | 6 (23.1) 13 | 11 (13.8) 20 |
| **AE by Toxicity** | | | |
| Grade 1 | 32 (59.3) 98 | 19 (73.1) 90 | 51 (63.8) 188 |
| Grade 2 | 19 (35.2) 35 | 16 (61.5) 46 | 35 (43.8) 81 |
| Grade 3 | 5 (9.3) 9 | 8 (30.8) 26 | 13 (16.3) 35 |
| Grade 4 | 1 (1.9) 1 | 1 (3.8) 3 | 2 (2.5) 4 |
| Grade 5 | 0 | 0 | 0 |
| **AE of Special Interest** | | | |

| | DAN/DAN<br>N = 54<br>n (%) E | Placebo/DAN<br>N = 26<br>n (%) E | Total<br>N = 80<br>n (%) E |
|---|---|---|---|
| Meningococcal Infections | 0 | 0 | 0 |
| Liver Enzyme Elevations | 1 (1.9) 3 | 1 (3.8) 1 | 2 (2.5) 4 |

Note: % = n/N × 100. DAN/DAN: Danicopan at Treatment Period 1 and Danicopan at Treatment Period 2; Placebo/DAN: Placebo at Treatment Period 1 and Danicopan at Treatment Period 2. A TEAE that had a start date that occurred during a certain Treatment Period is regarded as TEAE at that Treatment Period. Any TEAEs that lasted across treatment periods are only counted once in the treatment period the event started. Grade 1=mild; Grade 2=moderate; Grade 3=severe; Grade 4=life-threatening; Grade 5=Fatal. AEs are coded using MedDRA version 25.1.

Abbreviations: AE = adverse event; DAN = danicopan; E = events; N = number of participants; n = number of participants in each category; SAE = serious adverse event; TEAE= treatment-emergent adverse event

Pooled Studies

The table below provides an overview of all TEAEs in pooled studies data cutoff 31 Mar 2023.

**Table 84: Overview of All Treatment-Emergent Adverse Events in the Pooled Studies in Participants with PNH and C3G/IC-MPGN (Combined PNH and C3G/IC-MPGN Population) (data cutoff 31 Mar 2023)**

| Variable | PNH Add-on (N = 96) | | PNH Monotherapy (N = 10) | | All PNH (N = 106) | | C3G/IC-MPGN (N = 37) | | Combined PNH and C3G/IC-MPGN (N = 143) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | E | n (%) | E | n (%) | E | n (%) | E | n (%) | E |
| Any TEAE | 92 (95.8) | 868 | 10 (100) | 125 | 102 (96.2) | 993 | 34 (91.9) | 426 | 136 (95.1) | 1419 |
| Related TEAE | 25 (26.0) | 68 | 5 (50.0) | 12 | 30 (28.3) | 80 | 13 (35.1) | 39 | 43 (30.1) | 119 |
| Unrelated TEAE | 90 (93.8) | 800 | 10 (100) | 113 | 100 (94.3) | 913 | 34 (91.9) | 387 | 134 (93.7) | 1300 |
| Grade 1 | 80 (83.3) | 560 | 10 (100) | 86 | 90 (84.9) | 646 | 34 (91.9) | 351 | 124 (86.7) | 997 |
| Grade 2 | 69 (71.9) | 217 | 9 (90.0) | 33 | 78 (73.6) | 250 | 20 (54.1) | 59 | 98 (68.5) | 309 |
| Grade 3 | 38 (39.6) | 82 | 3 (30.0) | 5 | 41 (38.7) | 87 | 8 (21.6) | 16 | 49 (34.3) | 103 |
| Grade 4 | 6 (6.3) | 9 | 1 (10.0) | 1 | 7 (6.6) | 10 | 0 | 0 | 7 (4.9) | 10 |
| Grade 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TEAE leading to treatment/study discontinuation | 6 (6.3) | 8 | 1 (10.0) | 3 | 7 (6.6) | 11 | 2 (5.4) | 2 | 9 (6.3) | 13 |
| TEAE of special interest | 19 (19.8) | 34 | 1 (10.0) | 3 | 20 (18.9) | 37 | 3 (8.1) | 5 | 23 (16.1) | 42 |
| Meningococcal infections | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liver enzyme elevations | 19 (19.8) | 34 | 1 (10.0) | 3 | 20 (18.9) | 37 | 3 (8.1) | 5 | 23 (16.1) | 42 |
| Any treatment-emergent SAE | 26 (27.1) | 49 | 4 (40.0) | 8 | 30 (28.3) | 57 | 5 (13.5) | 6 | 35 (24.5) | 63 |
| Related SAE | 3 (3.1) | 4 | 1 (10.0) | 3 | 4 (3.8) | 7 | 1 (2.7) | 1 | 5 (3.5) | 8 |
| Unrelated SAE | 26 (27.1) | 45 | 3 (30.0) | 5 | 29 (27.4) | 50 | 4 (10.8) | 5 | 33 (23.1) | 55 |
| SAE leading to treatment/study discontinuation | 2 (2.1) | 3 | 1 (10.0) | 3 | 3 (2.8) | 6 | 1 (2.7) | 1 | 4 (2.8) | 7 |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Note: Percentages are based on the total number of participants in each column. Treatment-emergent AEs were AEs with a start date and start time on or after the date and time of the first dose of danicopan. Related AEs were defined as AEs that are possibly, probably, or definitely related to study intervention. Not related AEs were defined as AEs that are unlikely or not related to study intervention. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = fatal. AEs were coded using MedDRA Version 25.1. TEAEs of special interest included meningococcal infections and liver enzyme elevations. For Studies ACH471-100, ACH471-103, ACH471-101, ACH471-201, and ALXN2040-PNH-301, a TEAE leading to study discontinuation was defined as having a discontinuation reason of AE and the study treatment was either reduced, interrupted, or withdrawn. For Studies ACH471-204 and ACH471-205, a TEAE leading to study discontinuation was defined as having a discontinuation reason of AE.

Abbreviations: AE = adverse event; C3G = complement 3 glomerulopathy; E = number of events; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; TEAE = treatment-emergent adverse event

**Common Adverse Events**

Phase 3 PNH Study ALXN2040-PNH-301

The TEAEs reported in ≥ 5% of participants in danicopan group by MedDRA System Organ Class and Preferred Term for TP1 period 1 up to the clinical database cutoff date of 31 Mar 2023 are summarized in Table 85.

The percentage of participants with Grade 2 and Grade 3 events was similar between the add on danicopan group and the placebo group in TP1 (Data cut 31Mar2023). Grade 3 TEAEs were reported in 15.8% of participants in the add on danicopan group: anaemia, leukopenia, neutropenia, cholecystitis, cholelithiasis, COVID-19, ALT increased, AST increased, blood bilirubin increased, WBC count decreased, blood pressure increased, and neutrophil count decreased. Grade 3 TEAEs were reported in 13.8% of participants in the placebo group: anaemia, thrombocytopenia, and asthenia. One (1.8%) participant in the add on danicopan group experienced a Grade 4 SAE of pancreatitis that was assessed as related to study intervention and treatment was discontinued. There were no Grade 4 TEAEs in the placebo group and no Grade 5 TEAEs in either group as of Clinical Database cutoff date of 31 Mar 2023.

**Table 85: TEAEs Reported in ≥ 5% of Participants in Danicopan Group by MedDRA System Organ Class and Preferred Term for Treatment Period 1 Up to the Clinical Database Cutoff Date of 31 Mar 2023 (Study ALXN2040-PNH-301, Safety Analysis Set)**

| System Organ Class<br>Preferred Term | Danicopan<br>N = 57 | | Placebo<br>N = 29 | |
|---|---|---|---|---|
| | n (%) | E | n (%) | E |
| Any adverse event | 43 (75.4) | 141 | 18 (62.1) | 77 |
| Gastrointestinal disorders | 17 (29.8) | 27 | 9 (31.0) | 13 |
| Nausea | 5 (8.8) | 7 | 3 (10.3) | 3 |
| Diarrhoea | 4 (7.0) | 4 | 3 (10.3) | 4 |
| Vomiting | 3 (5.3) | 4 | 0 | 0 |
| General disorders and administration site conditions | 6 (10.5) | 11 | 6 (20.7) | 8 |
| Pyrexia | 3 (5.3) | 6 | 0 | 0 |
| Infections and infestations | 11 (19.3) | 13 | 7 (24.1) | 10 |
| Urinary tract infection | 3 (5.3) | 3 | 1 (3.4) | 2 |
| Investigations | 8 (14.0) | 25 | 4 (13.8) | 7 |
| Alanine aminotransferase increased | 3 (5.3) | 4 | 1 (3.4) | 1 |
| Musculoskeletal and connective tissue disorders | 10 (17.5) | 12 | 5 (17.2) | 5 |
| Arthralgia | 4 (7.0) | 4 | 2 (6.9) | 2 |
| Pain in extremity | 3 (5.3) | 3 | 0 | 0 |
| Nervous system disorders | 7 (12.3) | 10 | 5 (17.2) | 7 |
| Headache | 6 (10.5) | 8 | 3 (10.3) | 4 |
| Vascular disorders | 5 (8.8) | 5 | 3 (10.3) | 3 |
| Hypertension | 3 (5.3) | 3 | 1 (3.4) | 1 |

Note: In summarizing n (%), if a participant had multiple events for a particular SOC or Preferred Term, they were counted only once for that SOC or Preferred Term. SOCs are sorted alphabetically, and Preferred Terms are sorted by decreasing percent based on the danicopan column. SOCs and Preferred Terms were coded using MedDRA Version 25.1.

Abbreviations: E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Pooled Studies

The incidence of TEAEs was generally similar across the pooled treatment populations. The most commonly reported TEAEs in the Combined PNH and C3G/IC-MPGN Population are shown in Table below (cutoff date of 31 Mar 2023).

*PNH Add-on Population*

As of the cutoff date 31 Mar 2023, the PNH Add-on Population had 141.5 patient years of exposure, and 95.8% of participants reported at least 1 TEAE. The most frequently reported TEAE was COVID 19 (32.3% of participants), followed by pyrexia (25.0%), headache (19.8%), and pain in extremity (11.5%) (Table 86). Other common TEAEs reported by > 10% of participants included arthralgia, diarrhoea, fatigue, nausea, and upper respiratory tract infection. A total of 15.6%, 39.6%, and 34.4% of participants reported Grade 1, 2, and 3 TEAEs, respectively. In addition, 6 (6.3%) participants reported Grade 4 TEAEs: myelodysplastic syndrome, pancreatitis, pulmonary haemorrhage, pulmonary oedema (each experienced by 1 participant), and thrombocytopenia (experienced by 2 participants). There were no Grade 5 events.

*All PNH Population*

The type of events frequently reported was similar between the All PNH Population and the PNH Add-on Population (Table 86). The All PNH Population had 163.4 patient-years of exposure, and 96.2% of participants reported at least 1 TEAE (Data cut 31 Mar 2023). The most frequently reported TEAE was COVID 19 (29.2%). Other common TEAEs reported by > 10% of participants included pyrexia, headache, diarrhoea, nausea, upper respiratory tract infection, arthralgia, fatigue, and pain in extremity. A total of 15.1%, 41.5%, and 33.0% of participants reported Grade 1, 2, and 3 TEAEs, respectively. Seven (6.6%) participants reported Grade 4 events: 6 participants were from the PNH Add-on Population, and 1 participant from the PNH Monotherapy Population (AST increased).

*Combined PNH and C3G/IC-MPGN Population*

The Combined PNH and C3G/IC-MPGN Population had 211.7 patient-years of exposure, and 95.1% of participants reported at least 1 TEAE (Data cut 31 Mar 2023). The most frequently reported TEAE was pyrexia (27.3%). Other common TEAEs reported in > 10% of participants included headache, COVID-19, diarrhoea, nausea, fatigue, upper respiratory tract infection, arthralgia, oropharyngeal pain, vomiting, and pain in extremity (Table 86). The percentages of participants with Grade 1, 2, and 3 events were similar across populations, 18.9%, 41.3%, and 30.1% of participants reported Grade 1, 2, and 3 TEAEs, respectively. Grade 4 TEAEs (reported in 7 [4.9%] participants) were reported from the PNH Population. There were no Grade 5 events.

**Table 86: Treatment-Emergent Adverse Events Reported by ≥ 5% of Participants in the Combined PNH and C3G/IC-MPGN Population (Cutoff Date 31 Mar 2023)**

| System Organ Class<br>Preferred term | PNH Add-on (N = 96) | | PNH Monotherapy (N = 10) | | All PNH (N = 106) | | C3G/IC-MPGN (N = 37) | | Combined PNH and C3G/ IC-MPGN (N = 143) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| Total patient-years | NA | 141.5 | NA | 21.9 | NA | 163.4 | NA | 48.4 | NA | 211.7 |
| Participants with at least 1 TEAE | 92 (95.8) | 868 (613.5) | 10 (100) | 125 (571.3) | 102 (96.2) | 993 (607.8) | 34 (91.9) | 426 (880.8) | 136 (95.1) | 1419 (670.2) |
| Infections and infestations | 62 (64.6) | 128 (90.5) | 6 (60.0) | 19 (86.8) | 68 (64.2) | 147 (90.0) | 21 (56.8) | 69 (142.7) | 89 (62.2) | 216 (102.0) |
| COVID-19 | 31 (32.3) | 31 (21.9) | 0 | 0 | 31 (29.2) | 31 (19.0) | 0 | 0 | 31 (21.7) | 31 (14.6) |
| Upper respiratory tract infection | 10 (10.4) | 16 (11.3) | 5 (50.0) | 10 (45.7) | 15 (14.2) | 26 (15.9) | 3 (8.1) | 6 (12.4) | 18 (12.6) | 32 (15.1) |
| Gastroenteritis | 4 (4.2) | 4 (2.8) | 1 (10.0) | 1 (4.6) | 5 (4.7) | 5 (3.1) | 7 (18.9) | 12 (24.8) | 12 (8.4) | 17 (8.0) |
| Urinary tract infection | 9 (9.4) | 9 (6.4) | 0 | 0 | 9 (8.5) | 9 (5.5) | 3 (8.1) | 5 (10.3) | 12 (8.4) | 14 (6.6) |
| Nasopharyngitis | 7 (7.3) | 8 (5.7) | 0 | 0 | 7 (6.6) | 8 (4.9) | 4 (10.8) | 11 (22.7) | 11 (7.7) | 19 (9.0) |
| Pharyngitis | 1 (1.0) | 1 (0.7) | 1 (10.0) | 1 (4.6) | 2 (1.9) | 2 (1.2) | 6 (16.2) | 6 (12.4) | 8 (5.6) | 8 (3.8) |
| General disorders and administration site conditions | 48 (50.0) | 107 (75.6) | 6 (60.0) | 16 (73.1) | 54 (50.9) | 123 (75.3) | 21 (56.8) | 59 (122.0) | 75 (52.4) | 182 (86.0) |
| Pyrexia | 24 (25.0) | 37 (26.1) | 3 (30.0) | 4 (18.3) | 27 (25.5) | 41 (25.1) | 12 (32.4) | 19 (39.3) | 39 (27.3) | 60 (28.3) |
| Fatigue | 12 (12.5) | 16 (11.3) | 1 (10.0) | 3 (13.7) | 13 (12.3) | 19 (11.6) | 5 (13.5) | 7 (14.5) | 18 (12.6) | 26 (12.3) |
| Oedema peripheral | 3 (3.1) | 3 (2.1) | 1 (10.0) | 2 (9.1) | 4 (3.8) | 5 (3.1) | 9 (24.3) | 16 (33.1) | 13 (9.1) | 21 (9.9) |
| Asthenia | 8 (8.3) | 15 (10.6) | 0 | 0 | 8 (7.5) | 15 (9.2) | 4 (10.8) | 5 (10.3) | 12 (8.4) | 20 (9.4) |
| Gastrointestinal disorders | 47 (49.0) | 115 (81.3) | 8 (80.0) | 19 (86.8) | 55 (51.9) | 134 (82.0) | 15 (40.5) | 45 (93.0) | 70 (49.0) | 179 (84.5) |
| Diarrhoea | 14 (14.6) | 23 (16.3) | 1 (10.0) | 1 (4.6) | 15 (14.2) | 24 (14.7) | 9 (24.3) | 11 (22.7) | 24 (16.8) | 35 (16.5) |
| Nausea | 12 (12.5) | 16 (11.3) | 3 (30.0) | 3 (13.7) | 15 (14.2) | 19 (11.6) | 5 (13.5) | 7 (14.5) | 20 (14.0) | 26 (12.3) |
| Vomiting | 7 (7.3) | 9 (6.4) | 2 (20.0) | 2 (9.1) | 9 (8.5) | 11 (6.7) | 7 (18.9) | 9 (18.6) | 16 (11.2) | 20 (9.4) |
| Abdominal pain | 7 (7.3) | 10 (7.1) | 3 (30.0) | 3 (13.7) | 10 (9.4) | 13 (8.0) | 1 (2.7) | 2 (4.1) | 11 (7.7) | 15 (7.1) |

| System Organ Class<br>Preferred term | PNH Add-on (N = 96) | | PNH Monotherapy (N = 10) | | All PNH (N = 106) | | C3G/IC-MPGN (N = 37) | | Combined PNH and C3G/ IC-MPGN (N = 143) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| Constipation | 6 (6.3) | 8 (5.7) | 1 (10.0) | 1 (4.6) | 7 (6.6) | 9 (5.5) | 1 (2.7) | 2 (4.1) | 8 (5.6) | 11 (5.2) |
| Musculoskeletal and connective tissue disorders | 35 (36.5) | 80 (56.5) | 4 (40.0) | 7 (32.0) | 39 (36.8) | 87 (53.3) | 13 (35.1) | 32 (66.2) | 52 (36.4) | 119 (56.2) |
| Arthralgia | 14 (14.6) | 17 (12.0) | 0 | 0 | 14 (13.2) | 17 (10.4) | 2 (5.4) | 3 (6.2) | 16 (11.2) | 20 (9.4) |
| Pain in extremity | 11 (11.5) | 16 (11.3) | 0 | 0 | 11 (10.4) | 16 (9.8) | 4 (10.8) | 4 (8.3) | 15 (10.5) | 20 (9.4) |
| Back pain | 8 (8.3) | 8 (5.7) | 2 (20.0) | 2 (9.1) | 10 (9.4) | 10 (6.1) | 3 (8.1) | 3 (6.2) | 13 (9.1) | 13 (6.1) |
| Myalgia | 7 (7.3) | 10 (7.1) | 2 (20.0) | 3 (13.7) | 9 (8.5) | 13 (8.0) | 2 (5.4) | 3 (6.2) | 11 (7.7) | 16 (7.6) |
| Nervous system disorders | 26 (27.1) | 59 (41.7) | 7 (70.0) | 10 (45.7) | 33 (31.1) | 69 (42.2) | 16 (43.2) | 34 (70.3) | 49 (34.3) | 103 (48.6) |
| Headache | 19 (19.8) | 35 (24.7) | 7 (70.0) | 8 (36.6) | 26 (24.5) | 43 (26.3) | 7 (18.9) | 14 (28.9) | 33 (23.1) | 57 (26.9) |
| Dizziness | 7 (7.3) | 7 (4.9) | 0 | 0 | 7 (6.6) | 7 (4.3) | 6 (16.2) | 7 (14.5) | 13 (9.1) | 14 (6.6) |
| Respiratory, thoracic, and mediastinal disorders | 31 (32.3) | 47 (33.2) | 2 (20.0) | 2 (9.1) | 33 (31.1) | 49 (30.0) | 14 (37.8) | 36 (74.4) | 47 (32.9) | 85 (40.1) |
| Oropharyngeal pain | 8 (8.3) | 8 (5.7) | 1 (10.0) | 1 (4.6) | 9 (8.5) | 9 (5.5) | 7 (18.9) | 10 (20.7) | 16 (11.2) | 19 (9.0) |
| Cough | 8 (8.3) | 8 (5.7) | 0 | 0 | 8 (7.5) | 8 (4.9) | 4 (10.8) | 5 (10.3) | 12 (8.4) | 13 (6.1) |
| Dyspnoea | 6 (6.3) | 6 (4.2) | 0 | 0 | 6 (5.7) | 6 (3.7) | 4 (10.8) | 5 (10.3) | 10 (7.0) | 11 (5.2) |
| Investigations | 28 (29.2) | 71 (50.2) | 1 (10.0) | 3 (13.7) | 29 (27.4) | 74 (45.3) | 15 (40.5) | 31 (64.1) | 44 (30.8) | 105 (49.6) |
| Alanine aminotransferase increased | 6 (6.3) | 7 (4.9) | 1 (10.0) | 2 (9.1) | 7 (6.6) | 9 (5.5) | 1 (2.7) | 1 (2.1) | 8 (5.6) | 10 (4.7) |
| Blood and lymphatic system disorders | 27 (28.1) | 62 (43.8) | 5 (50.0) | 10 (45.7) | 32 (30.2) | 72 (44.1) | 10 (27.0) | 14 (28.9) | 42 (29.4) | 86 (40.6) |
| Anaemia | 7 (7.3) | 9 (6.4) | 0 | 0 | 7 (6.6) | 9 (5.5) | 7 (18.9) | 7 (14.5) | 14 (9.8) | 16 (7.6) |
| Breakthrough haemolysis | 6 (6.3) | 7 (4.9) | 4 (40.0) | 8 (36.6) | 10 (9.4) | 15 (9.2) | 0 | 0 | 10 (7.0) | 15 (7.1) |
| Haemolysis | 7 (7.3) | 9 (6.4) | 1 (10.0) | 2 (9.1) | 8 (7.5) | 11 (6.7) | 0 | 0 | 8 (5.6) | 11 (5.2) |
| Neutropenia | 8 (8.3) | 10 (7.1) | 0 | 0 | 8 (7.5) | 10 (6.1) | 0 | 0 | 8 (5.6) | 10 (4.7) |
| Injury, poisoning and procedural complications | 19 (19.8) | 38 (26.9) | 4 (40.0) | 10 (45.7) | 23 (21.7) | 48 (29.4) | 5 (13.5) | 6 (12.4) | 28 (19.6) | 54 (25.5) |
| Contusion | 6 (6.3) | 10 (7.1) | 1 (10.0) | 1 (4.6) | 7 (6.6) | 11 (6.7) | 1 (2.7) | 1 (2.1) | 8 (5.6) | 12 (5.7) |
| Psychiatric disorders | 13 (13.5) | 18 (12.7) | 1 (10.0) | 1 (4.6) | 14 (13.2) | 19 (11.6) | 2 (5.4) | 3 (6.2) | 16 (11.2) | 22 (10.4) |
| Insomnia | 8 (8.3) | 8 (5.7) | 0 | 0 | 8 (7.5) | 8 (4.9) | 0 | 0 | 8 (5.6) | 8 (3.8) |

Note: Table presents TEAEs reported in ≥ 5% of participants of the Combined PNH and C3G/IC-MPGN Population. For the number of participants with at least 1 TEAE, all TEAEs were considered, including TEAEs reported in < 5% of the participants. Percentages are based on the total number of participants in each column. Rate of AEs is adjusted by patient-years of exposure, defined as (number of events)/100 patient-years. Treatment-emergent AEs were AEs with a start date and start time on or after the date and time of the first dose of danicopan. Under participant count columns, n (%), if a participant had more than 1 event for a particular SOC, the participant was counted only once for that SOC under n (%). If a participant had more than 1 event for a particular Preferred Term, the participant was counted only once for that Preferred Term. AEs were coded using MedDRA Version 25.1.

Abbreviations: AE = adverse event; C3G = complement 3 glomerulopathy; COVID-19 = coronavirus disease 2019; E = number of events; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; SOC = System Organ Class; TEAE = treatment-emergent adverse event

**TEAEs by danicopan Dose Level**

The incidence of TEAEs in the PNH Add-on Population appeared not to be dose dependent (table below). Participants could be in multiple danicopan dose groups, based on the dosage regimen they received during the study. Overall, the majority of the participants received a starting dose of 150 mg tid. All participants could be escalated to the next dose level according to protocol-specified requirements.

As of the Clinical Database cutoff date of 31 Mar 2023, 92.3%, 76.8%, and 92.5% of participants reported a TEAE while on danicopan 100 mg tid, 150 mg tid, and 200 mg tid, respectively, in the PNH Add-on Population (Table below).

**Table 87: Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events Up to the Clinical Database Cutoff Date of 31 Mar 2023 (PNH Add-on Population)**

| | 100 mg tid (N = 13) | | 150 mg tid (N = 95) | | 200 mg tid (N = 67) | | Total (N = 96) | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | E | n (%) | E | n (%) | E | n (%) | E |
| Any TEAE | 12 (92.3) | 87 | 73 (76.8) | 323 | 62 (92.5) | 458 | 92 (95.8) | 868 |
| Related TEAE | 4 (30.8) | 5 | 20 (21.1) | 49 | 6 (9.0) | 14 | 25 (26.0) | 68 |
| Unrelated TEAE | 10 (76.9) | 82 | 67 (70.5) | 274 | 61 (91.0) | 444 | 90 (93.8) | 800 |
| Grade 1 | 11 (84.6) | 63 | 61 (64.2) | 210 | 53 (79.1) | 287 | 80 (83.3) | 560 |
| Grade 2 | 6 (46.2) | 19 | 40 (42.1) | 83 | 39 (58.2) | 115 | 69 (71.9) | 217 |
| Grade 3 | 4 (30.8) | 4 | 19 (20.0) | 28 | 19 (28.4) | 50 | 38 (39.6) | 82 |
| Grade 4 | 1 (7.7) | 1 | 2 (2.1) | 2 | 4 (6.0) | 6 | 6 (6.3) | 9 |
| Grade 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TEAE leading to treatment/study discontinuation | 1 (7.7) | 1 | 3 (3.2) | 5 | 2 (3.0) | 2 | 6 (6.3) | 8 |
| TEAE of special interest | 4 (30.8) | 7 | 12 (12.6) | 17 | 5 (7.5) | 10 | 19 (19.8) | 34 |
| Meningococcal infections | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liver enzyme elevations | 4 (30.8) | 7 | 12 (12.6) | 17 | 5 (7.5) | 10 | 19 (19.8) | 34 |
| Any treatment-emergent SAE | 2 (15.4) | 3 | 11 (11.6) | 14 | 16 (23.9) | 32 | 26 (27.1) | 49 |
| Related SAE | 1 (7.7) | 1 | 2 (2.1) | 3 | 0 | 0 | 3 (3.1) | 4 |
| Unrelated SAE | 2 (15.4) | 2 | 10 (10.5) | 11 | 16 (23.9) | 32 | 26 (27.1) | 45 |
| SAE leading to treatment/study discontinuation | 1 (7.7) | 1 | 1 (1.1) | 2 | 0 | 0 | 2 (2.1) | 3 |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Note: Percentages are based on the total number of participants in each column. Participants could have been counted under more than 1 column based on the dosage regimen received. All participants were counted once in the "Total" column. Treatment-emergent AEs were AEs with a start date and start time on or after the date and time of the first dose of danicopan. Related AEs were defined as AEs that are possibly, probably, or definitely related to study intervention. Not related AEs were defined as AEs that are unlikely or not related to study intervention. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = fatal. AEs were coded using MedDRA Version 25.1. For Studies ACH471-100, ACH471-103, ACH471-101, ACH471-201, and ALXN2040-PNH-301, a TEAE leading to study discontinuation was defined as having a discontinuation reason of AE and the study treatment was either reduced, interrupted, or withdrawn. For Studies ACH471-204 and ACH471-205, a TEAE leading to study discontinuation was defined as having a discontinuation reason of AE.

Abbreviations: AE = adverse event; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; TEAE = treatment-emergent adverse event; tid = 3 times daily

There was no clear trend seen between TEAE severity and dose in participants on 100, 150, or 200 mg tid danicopan.

There was no increase in incidence of related TEAEs with increasing dose in the PNH Add-on Population. There seems to be a higher incidence of related TEAEs while participants were on 100 mg tid (30.8% of participants) than when they were on 150 or 200 mg tid (21.1% and 9.0%, respectively); this is due to the much smaller sample size of participants who were on 100 mg tid (Table below).

**Table 88: Treatment-Emergent Adverse Events Reported by ≥ 5% of Participants of the PNH Add-on Population by Dose Up to the Clinical Database Cutoff Date of 31 Mar 2023 (PNH Add-on Population)**

| System Organ Class<br>Preferred Term | 100 mg tid<br>(N = 13) | | 150 mg tid<br>(N = 95) | | 200 mg tid<br>(N = 67) | | Total<br>(N = 96) | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| Total patient-years | NA | 6.7 | NA | 52.1 | NA | 82.7 | NA | 141.5 |
| Participants with at least 1 TEAE | 12 (92.3) | 87 (1291.6) | 73 (76.8) | 323 (619.9) | 62 (92.5) | 458 (554.1) | 92 (95.8) | 868 (613.5) |
| Infections and infestations | 3 (23.1) | 5 (74.2) | 29 (30.5) | 49 (94.0) | 40 (59.7) | 74 (89.5) | 62 (64.6) | 128 (90.5) |
| COVID-19 | 0 | 0 | 9 (9.5) | 9 (17.3) | 22 (32.8) | 22 (26.6) | 31 (32.3) | 31 (21.9) |
| Upper respiratory tract infection | 3 (23.1) | 4 (59.4) | 4 (4.2) | 4 (7.7) | 6 (9.0) | 8 (9.7) | 10 (10.4) | 16 (11.3) |
| Urinary tract infection | 0 | 0 | 5 (5.3) | 5 (9.6) | 4 (6.0) | 4 (4.8) | 9 (9.4) | 9 (6.4) |
| Nasopharyngitis | 0 | 0 | 2 (2.1) | 2 (3.8) | 5 (7.5) | 6 (7.3) | 7 (7.3) | 8 (5.7) |
| General disorders and administration site conditions | 6 (46.2) | 14 (207.8) | 20 (21.1) | 34 (65.3) | 29 (43.3) | 59 (71.4) | 48 (50.0) | 107 (75.6) |
| Pyrexia | 3 (23.1) | 4 (59.4) | 7 (7.4) | 11 (21.1) | 17 (25.4) | 22 (26.6) | 24 (25.0) | 37 (26.1) |
| Fatigue | 2 (15.4) | 3 (44.5) | 4 (4.2) | 4 (7.7) | 8 (11.9) | 9 (10.9) | 12 (12.5) | 16 (11.3) |
| Asthenia | 0 | 0 | 3 (3.2) | 4 (7.7) | 5 (7.5) | 11 (13.3) | 8 (8.3) | 15 (10.6) |
| Influenza like illness | 0 | 0 | 1 (1.1) | 1 (1.9) | 5 (7.5) | 5 (6.0) | 5 (5.2) | 6 (4.2) |
| Gastrointestinal disorders | 6 (46.2) | 17 (252.4) | 27 (28.4) | 41 (78.7) | 24 (35.8) | 57 (69.0) | 47 (49.0) | 115 (81.3) |
| Diarrhoea | 1 (7.7) | 1 (14.8) | 7 (7.4) | 8 (15.4) | 8 (11.9) | 14 (16.9) | 14 (14.6) | 23 (16.3) |
| Nausea | 2 (15.4) | 2 (29.7) | 6 (6.3) | 8 (15.4) | 4 (6.0) | 6 (7.3) | 12 (12.5) | 16 (11.3) |
| Abdominal pain | 3 (23.1) | 4 (59.4) | 2 (2.1) | 2 (3.8) | 3 (4.5) | 4 (4.8) | 7 (7.3) | 10 (7.1) |
| Vomiting | 1 (7.7) | 1 (14.8) | 3 (3.2) | 4 (7.7) | 4 (6.0) | 4 (4.8) | 7 (7.3) | 9 (6.4) |
| Constipation | 0 | 0 | 5 (5.3) | 5 (9.6) | 3 (4.5) | 3 (3.6) | 6 (6.3) | 8 (5.7) |
| Abdominal pain upper | 1 (7.7) | 2 (29.7) | 1 (1.1) | 1 (1.9) | 3 (4.5) | 3 (3.6) | 5 (5.2) | 6 (4.2) |

| System Organ Class<br>Preferred Term | 100 mg tid<br>(N = 13) | | 150 mg tid<br>(N = 95) | | 200 mg tid<br>(N = 67) | | Total<br>(N = 96) | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| Musculoskeletal and connective tissue disorders | 6 (46.2) | 11 (163.3) | 16 (16.8) | 28 (53.7) | 19 (28.4) | 41 (49.6) | 35 (36.5) | 80 (56.5) |
| Arthralgia | 4 (30.8) | 4 (59.4) | 5 (5.3) | 6 (11.5) | 7 (10.4) | 7 (8.5) | 14 (14.6) | 17 (12.0) |
| Pain in extremity | 2 (15.4) | 2 (29.7) | 5 (5.3) | 7 (13.4) | 6 (9.0) | 7 (8.5) | 11 (11.5) | 16 (11.3) |
| Back pain | 0 | 0 | 2 (2.1) | 2 (3.8) | 6 (9.0) | 6 (7.3) | 8 (8.3) | 8 (5.7) |
| Myalgia | 1 (7.7) | 1 (14.8) | 3 (3.2) | 3 (5.8) | 3 (4.5) | 6 (7.3) | 7 (7.3) | 10 (7.1) |
| Respiratory, thoracic and mediastinal disorders | 4 (30.8) | 5 (74.2) | 13 (13.7) | 16 (30.7) | 17 (25.4) | 26 (31.5) | 31 (32.3) | 47 (33.2) |
| Cough | 0 | 0 | 3 (3.2) | 3 (5.8) | 5 (7.5) | 5 (6.0) | 8 (8.3) | 8 (5.7) |
| Oropharyngeal pain | 1 (7.7) | 1 (14.8) | 3 (3.2) | 3 (5.8) | 4 (6.0) | 4 (4.8) | 8 (8.3) | 8 (5.7) |
| Dyspnoea | 1 (7.7) | 1 (14.8) | 3 (3.2) | 3 (5.8) | 2 (3.0) | 2 (2.4) | 6 (6.3) | 6 (4.2) |
| Investigations | 5 (38.5) | 8 (118.8) | 12 (12.6) | 29 (55.7) | 13 (19.4) | 34 (41.1) | 28 (29.2) | 71 (50.2) |
| Alanine aminotransferase increased | 3 (23.1) | 3 (44.5) | 3 (3.2) | 4 (7.7) | 0 | 0 | 6 (6.3) | 7 (4.9) |
| Blood and lymphatic system disorders | 2 (15.4) | 2 (29.7) | 15 (15.8) | 21 (40.3) | 17 (25.4) | 39 (47.2) | 27 (28.1) | 62 (43.8) |
| Neutropenia | 0 | 0 | 5 (5.3) | 6 (11.5) | 3 (4.5) | 4 (4.8) | 8 (8.3) | 10 (7.1) |
| Anaemia | 1 (7.7) | 1 (14.8) | 3 (3.2) | 3 (5.8) | 3 (4.5) | 5 (6.0) | 7 (7.3) | 9 (6.4) |
| Haemolysis | 1 (7.7) | 1 (14.8) | 4 (4.2) | 6 (11.5) | 2 (3.0) | 2 (2.4) | 7 (7.3) | 9 (6.4) |
| Breakthrough haemolysis | 0 | 0 | 0 | 0 | 6 (9.0) | 7 (8.5) | 6 (6.3) | 7 (4.9) |
| Thrombocytopenia | 0 | 0 | 3 (3.2) | 3 (5.8) | 4 (6.0) | 14 (16.9) | 5 (5.2) | 17 (12.0) |
| Nervous system disorders | 4 (30.8) | 10 (148.5) | 12 (12.6) | 23 (44.1) | 17 (25.4) | 26 (31.5) | 26 (27.1) | 59 (41.7) |
| Headache | 3 (23.1) | 6 (89.1) | 9 (9.5) | 13 (25.0) | 12 (17.9) | 16 (19.4) | 19 (19.8) | 35 (24.7) |
| Dizziness | 1 (7.7) | 1 (14.8) | 2 (2.1) | 2 (3.8) | 4 (6.0) | 4 (4.8) | 7 (7.3) | 7 (4.9) |

| System Organ Class<br>Preferred Term | 100 mg tid<br>(N = 13) | | 150 mg tid<br>(N = 95) | | 200 mg tid<br>(N = 67) | | Total<br>(N = 96) | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| njury, poisoning and procedural complications | 2 (15.4) | 4 (59.4) | 13 (13.7) | 18 (34.5) | 10 (14.9) | 16 (19.4) | 19 (19.8) | 38 (26.9) |
| Contusion | 2 (15.4) | 2 (29.7) | 2 (2.1) | 2 (3.8) | 3 (4.5) | 6 (7.3) | 6 (6.3) | 10 (7.1) |
| Psychiatric disorders | 3 (23.1) | 4 (59.4) | 3 (3.2) | 3 (5.8) | 9 (13.4) | 11 (13.3) | 13 (13.5) | 18 (12.7) |
| Insomnia | 0 | 0 | 2 (2.1) | 2 (3.8) | 6 (9.0) | 6 (7.3) | 8 (8.3) | 8 (5.7) |

Note: Table presents TEAEs reported in ≥ 5% of participants of the PNH Add-on Population. For the number of participants with at least 1 TEAE, all TEAEs were considered, including TEAEs reported by < 5% of the participants. Percentages are based on the total number of participants in each column. Participants could have been counted under more than 1 column based on the dosage regimen received. All participants are counted once in the "Total" column. Rate of AEs is adjusted by patient-years of exposure, defined as (number of events)/100 patient-years. Treatment-emergent AEs are AEs with a start date and start time on or after the date and time of the first dose of danicopan. Under participant count columns, n (%), if a participant had more than 1 event for a particular SOC, the participant was counted only once for that SOC under n (%). If a participant had more than 1 event for a particular Preferred Term, the participant was counted only once for that Preferred Term. AEs were coded using MedDRA Version 25.1.

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; SOC = System Organ Class; TEAE = treatment-emergent adverse event; tid = 3 times daily

### TEAEs by treatment duration

Overall, the safety profile of danicopan remained stable with no increased incidence or rate of TEAEs over time. The onset of new TEAEs were most often reported during the first 12 weeks of treatment, including TEAEs associated with liver enzyme abnormalities. (Table below)

**Table 89: Treatment-Emergent Adverse Events Reported by ≥ 5% of Participants of the Combined PNH and C3G/IC-MPGN Population by Time Interval (Combined PNH and C3G/IC-MPGN Population) (Cutoff Date of 31 Mar 2023)**

| System Organ Class<br>Preferred term | 0 to 12 Weeks<br>(N = 143) | | > 12-24 Weeks<br>(N = 132) | | > 24-48 Weeks<br>(N = 130) | | > 48 Weeks<br>(N = 103) | | Total<br>(N = 143) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| Total patient-years | NA | 31.6 | NA | 30.0 | NA | 54.3 | NA | 95.8 | NA | 211.7 |
| Participants with at least 1 TEAE | 112 (78.3) | 471 (1488.9) | 97 (73.5) | 298 (994.0) | 85 (65.4) | 283 (520.9) | 75 (72.8) | 367 (383.1) | 136 (95.1) | 1419 (670.2) |
| Infections and infestations | 39 (27.3) | 49 (154.9) | 33 (25.0) | 42 (140.1) | 39 (30.0) | 57 (104.9) | 40 (38.8) | 68 (71.0) | 89 (62.2) | 216 (102.0) |
| COVID-19 | 4 (2.8) | 4 (12.6) | 2 (1.5) | 2 (6.7) | 12 (9.2) | 12 (22.1) | 13 (12.6) | 13 (13.6) | 31 (21.7) | 31 (14.6) |
| Upper respiratory tract infection | 9 (6.3) | 10 (31.6) | 5 (3.8) | 6 (20.0) | 7 (5.4) | 7 (12.9) | 9 (8.7) | 9 (9.4) | 18 (12.6) | 32 (15.1) |
| Gastroenteritis | 2 (1.4) | 2 (6.3) | 5 (3.8) | 6 (20.0) | 4 (3.1) | 4 (7.4) | 5 (4.9) | 5 (5.2) | 12 (8.4) | 17 (8.0) |
| Urinary tract infection | 5 (3.5) | 5 (15.8) | 1 (0.8) | 1 (3.3) | 1 (0.8) | 1 (1.8) | 5 (4.9) | 7 (7.3) | 12 (8.4) | 14 (6.6) |
| Nasopharyngitis | 5 (3.5) | 6 (19.0) | 2 (1.5) | 2 (6.7) | 7 (5.4) | 8 (14.7) | 3 (2.9) | 3 (3.1) | 11 (7.7) | 19 (9.0) |
| Pharyngitis | 3 (2.1) | 3 (9.5) | 2 (1.5) | 2 (6.7) | 1 (0.8) | 1 (1.8) | 2 (1.9) | 2 (2.1) | 8 (5.6) | 8 (3.8) |
| General disorders and administration site conditions | 32 (22.4) | 52 (164.4) | 30 (22.7) | 42 (140.1) | 30 (23.1) | 43 (79.1) | 27 (26.2) | 45 (47.0) | 75 (52.4) | 182 (86.0) |
| Pyrexia | 8 (5.6) | 11 (34.8) | 10 (7.6) | 15 (50.0) | 12 (9.2) | 14 (25.8) | 18 (17.5) | 20 (20.9) | 39 (27.3) | 60 (28.3) |
| Fatigue | 10 (7.0) | 11 (34.8) | 6 (4.5) | 6 (20.0) | 5 (3.8) | 5 (9.2) | 4 (3.9) | 4 (4.2) | 18 (12.6) | 26 (12.3) |
| Oedema peripheral | 6 (4.2) | 10 (31.6) | 4 (3.0) | 4 (13.3) | 5 (3.8) | 5 (9.2) | 2 (1.9) | 2 (2.1) | 13 (9.1) | 21 (9.9) |
| Asthenia | 3 (2.1) | 4 (12.6) | 4 (3.0) | 4 (13.3) | 6 (4.6) | 7 (12.9) | 4 (3.9) | 5 (5.2) | 12 (8.4) | 20 (9.4) |
| Gastrointestinal disorders | 44 (30.8) | 79 (249.7) | 24 (18.2) | 38 (126.8) | 16 (12.3) | 24 (44.2) | 22 (21.4) | 38 (39.7) | 70 (49.0) | 179 (84.5) |
| Diarrhoea | 11 (7.7) | 12 (37.9) | 12 (9.1) | 14 (46.7) | 3 (2.3) | 3 (5.5) | 4 (3.9) | 6 (6.3) | 24 (16.8) | 35 (16.5) |
| Nausea | 13 (9.1) | 15 (47.4) | 4 (3.0) | 4 (13.3) | 4 (3.1) | 5 (9.2) | 2 (1.9) | 2 (2.1) | 20 (14.0) | 26 (12.3) |
| Vomiting | 7 (4.9) | 8 (25.3) | 5 (3.8) | 5 (16.7) | 3 (2.3) | 3 (5.5) | 4 (3.9) | 4 (4.2) | 16 (11.2) | 20 (9.4) |
| Abdominal pain | 6 (4.2) | 7 (22.1) | 2 (1.5) | 2 (6.7) | 3 (2.3) | 4 (7.4) | 2 (1.9) | 2 (2.1) | 11 (7.7) | 15 (7.1) |
| Constipation | 5 (3.5) | 5 (15.8) | 3 (2.3) | 3 (10.0) | 0 | 0 | 3 (2.9) | 3 (3.1) | 8 (5.6) | 11 (5.2) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | 28 (19.6) | 37 (117.0) | 18 (13.6) | 23 (76.7) | 7 (13.1) | 29 (53.4) | 18 (17.5) | 30 (31.3) | 52 (36.4) | 119 (56.2) |
| Arthralgia | 10 (7.0) | 10 (31.6) | 1 (0.8) | 1 (3.3) | 3 (2.3) | 3 (5.5) | 5 (4.9) | 6 (6.3) | 16 (11.2) | 20 (9.4) |
| Pain in extremity | 4 (2.8) | 4 (12.6) | 2 (1.5) | 2 (6.7) | 9 (6.9) | 10 (18.4) | 4 (3.9) | 4 (4.2) | 15 (10.5) | 20 (9.4) |
| Back pain | 3 (2.1) | 3 (9.5) | 3 (2.3) | 3 (10.0) | 5 (3.8) | 5 (9.2) | 2 (1.9) | 2 (2.1) | 13 (9.1) | 13 (6.1) |
| Myalgia | 6 (4.2) | 7 (22.1) | 2 (1.5) | 3 (10.0) | 2 (1.5) | 2 (3.7) | 4 (3.9) | 4 (4.2) | 11 (7.7) | 16 (7.6) |
| Nervous system disorders | 27 (18.9) | 42 (132.8) | 17 (12.9) | 21 (70.0) | 7 (5.4) | 9 (16.6) | 19 (18.4) | 31 (32.4) | 49 (34.3) | 103 (48.6) |
| Headache | 9 (13.3) | 25 (79.0) | 10 (7.6) | 14 (46.7) | 3 (2.3) | 3 (5.5) | 11 (10.7) | 15 (15.7) | 33 (23.1) | 57 (26.9) |
| Dizziness | 6 (4.2) | 7 (22.1) | 3 (2.3) | 3 (10.0) | 2 (1.5) | 2 (3.7) | 2 (1.9) | 2 (2.1) | 13 (9.1) | 14 (6.6) |
| Respiratory, thoracic and mediastinal disorders | 21 (14.7) | 30 (94.8) | 15 (11.4) | 18 (60.0) | 11 (8.5) | 14 (25.8) | 16 (15.5) | 23 (24.0) | 47 (32.9) | 85 (40.1) |
| Oropharyngeal pain | 7 (4.9) | 7 (22.1) | 4 (3.0) | 4 (13.3) | 3 (2.3) | 3 (5.5) | 5 (4.9) | 5 (5.2) | 16 (11.2) | 19 (9.0) |
| Cough | 4 (2.8) | 5 (15.8) | 2 (1.5) | 2 (6.7) | 1 (0.8) | 1 (1.8) | 5 (4.9) | 5 (5.2) | 12 (8.4) | 13 (6.1) |
| Dyspnoea | 1 (0.7) | 1 (3.2) | 4 (3.0) | 4 (13.3) | 2 (1.5) | 2 (3.7) | 4 (3.9) | 4 (4.2) | 10 (7.0) | 11 (5.2) |
| Investigations | 19 (13.3) | 46 (145.4) | 16 (12.1) | 24 (80.1) | 14 (10.8) | 18 (33.1) | 10 (9.7) | 17 (17.7) | 44 (30.8) | 105 (49.6) |
| Alanine aminotransferase increased | 6 (4.2) | 8 (25.3) | 1 (0.8) | 1 (3.3) | 1 (0.8) | 1 (1.8) | 0 | 0 | 8 (5.6) | 10 (4.7) |
| Blood and lymphatic system disorders | 19 (13.3) | 24 (75.9) | 12 (9.1) | 14 (46.7) | 13 (10.0) | 23 (42.3) | 14 (13.6) | 25 (26.1) | 42 (29.4) | 86 (40.6) |
| Anaemia | 5 (3.5) | 5 (15.8) | 4 (3.0) | 4 (13.3) | 3 (2.3) | 4 (7.4) | 3 (2.9) | 3 (3.1) | 14 (9.8) | 16 (7.6) |
| Breakthrough haemolysis | 1 (0.7) | 2 (6.3) | 2 (1.5) | 2 (6.7) | 4 (3.1) | 4 (7.4) | 5 (4.9) | 7 (7.3) | 10 (7.0) | 15 (7.1) |
| Haemolysis | 5 (3.5) | 6 (19.0) | 3 (2.3) | 3 (10.0) | 2 (1.5) | 2 (3.7) | 0 | 0 | 8 (5.6) | 11 (5.2) |
| Neutropenia | 3 (2.1) | 4 (12.6) | 4 (3.0) | 4 (13.3) | 1 (0.8) | 1 (1.8) | 1 (1.0) | 1 (1.0) | 8 (5.6) | 10 (4.7) |
| Injury, poisoning and procedural complications | 15 (10.5) | 19 (60.1) | 8 (6.1) | 12 (40.0) | 8 (6.2) | 11 (20.2) | 8 (7.8) | 12 (12.5) | 28 (19.6) | 54 (25.5) |
| Contusion | 6 (4.2) | 6 (19.0) | 1 (0.8) | 3 (10.0) | 2 (1.5) | 2 (3.7) | 1 (1.0) | 1 (1.0) | 8 (5.6) | 12 (5.7) |
| Psychiatric disorders | 7 (4.9) | 8 (25.3) | 5 (3.8) | 5 (16.7) | 2 (1.5) | 3 (5.5) | 5 (4.9) | 6 (6.3) | 16 (11.2) | 22 (10.4) |
| Insomnia | 2 (1.4) | 2 (6.3) | 2 (1.5) | 2 (6.7) | 1 (0.8) | 1 (1.8) | 3 (2.9) | 3 (3.1) | 8 (5.6) | 8 (3.8) |

Note: Table presents TEAEs reported by ≥ 5% of participants of the Combined PNH and C3G/IC-MPGN Population. For the number of participants with at least 1 TEAE, all TEAEs were considered, including TEAEs reported by < 5% of the participants.
Note: Percentages are based on the total number of participants in each column. Participants could have been counted under more than 1 column based on the treatment duration. All participants are counted once in the "Total" column.
Rate of AEs is adjusted by patient-years of exposure, defined as (number of events)/100 patient-years.
Treatment-emergent AEs are AEs with a start date and start time on or after the date and time of the first dose of danicopan.
Under participant count columns, n (%), if a participant had more than 1 event for a particular SOC, the participant is counted only once for that SOC under n (%). If a participant had more than 1 event for a particular PT, the participant is counted only once for that PT.
AEs were coded using MedDRA Version 25.1.
AEs occurring after the last dose of danicopan are analyzed as occurring on the last dose date.
Abbreviations: AE = adverse event; C3G = complement 3 glomerulopathy; COVID-19 = coronavirus disease 2019; E = number of events; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; PNH = paroxysmal nocturnal hemoglobinuria; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

**TEAEs by relationship**

Phase 3 PNH Study ALXN2040-PNH-301

Related TEAEs reported in ≥ 2% of participants treated with add-on danicopan in Study ALXN2040-PNH-301 as of the data cutoff date of 31 Mar 2023 are provided in **Table 90** for TP1 and **Table 91** for LTE by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). No related TEAEs in TP2 were reported in ≥ 2% of participants.

In TP1, the incidence of TEAEs assessed as related to study drug by the Investigator was higher in the add-on placebo group (27.6%) as compared to the add-on danicopan group (21.1%). Related TEAEs reported only in ≥ 2% of participants in the add-on danicopan group in TP1 were pyrexia, alanine aminotransferase (ALT) increased, and headache. The related events of pyrexia reported in TP1 resolved without treatment modification and had confounding factors or alternative aetiology. The other related events reported in ≥ 2% of participants in TP1 (nausea and aspartate aminotransferase (AST) increased) had a similar incidence between treatment groups or a higher incidence in the add-on placebo group.

The most frequently reported treatment-related TEAEs in the add-on danicopan group in TP1 period (> 3% of participants) were nausea (7.0%), pyrexia, ALT increased, AST increased, and headache (3.5%

each) (data cutoff 31 Mar 2023). The only related TEAE reported in ≥ 2% of participants in the LTE period was thrombocytopenia. Those were reported in 2 (2.5%) participants. Both events were confounded; 1 participant had a relevant medical history of aplastic anaemia, and the other reported a concurrent TEAE of myelodysplastic syndrome. Both events were non-serious and resolved without modification to study drug, and no plausible temporal association with add-on danicopan was observed.

**Table 90: Study ALXN2040-PNH-301 Treatment Period 1 Related Treatment-Emergent Adverse Events Reported in ≥ 2% of Participants Treated with Add-On Danicopan (Data Cutoff Date 31 Mar 2023)**

| **System Organ Class**<br>**Preferred Term** | **Danicopan**<br>**N = 57**<br>**n (%)** | **Placebo**<br>**N = 29**<br>**n (%)** |
|---|---|---|
| Any Related Adverse Event | 12 (21.1) | 8 (27.6) |
| Gastrointestinal disorders | 5 (8.8) | 3 (10.3) |
| Nausea | 4 (7.0) | 2 (6.9) |
| General Disorders and administration site conditions | 2 (3.5) | 0 |
| Pyrexia | 2 (3.5) | 0 |
| Investigations | 4 (7.0) | 3 (10.3) |
| Alanine aminotransferase increased | 2 (3.5) | 0 |
| Aspartate aminotransferase increased | 2 (3.5) | 2 (6.9) |
| Nervous system disorders | 2 (3.5) | 2 (6.9) |
| Headache | 2 (3.5) | 0 |

Note: % = n/N × 100. A TEAE that had a start date that occurred during a certain Treatment Period is regarded as TEAE at that Treatment Period. Any TEAEs that lasted across treatment periods are only counted once in the treatment period the event started. If a participant had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT. Highest relationship for each patient per SOC/PT is summarized. SOCs are sorted alphabetically, and PTs are sorted by decreasing percent based on Total column. SOCs and PTs were coded using MedDRA version 25.1.
Abbreviations: N = number of participants; n = number of participants in each category; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event

**Table 91: Study ALXN2040-PNH-301 LTE Related Treatment-Emergent Adverse Events Reported in ≥ 2% of Participants (Data Cutoff Date 31 Mar 2023)**

| System Organ Class<br>Preferred Term | DAN/DAN<br>N = 54<br>n (%) | Placebo/DAN<br>N = 26<br>n (%) | Total<br>N = 80<br>n (%) |
|---|---|---|---|
| Any Adverse Event | 2 (3.7) | 4 (15.4) | 6 (7.5) |
| Blood and lymphatic disorders | 0 | 2 (7.7) | 2 (2.5) |
| Thrombocytopenia | 0 | 2 (7.7) | 2 (2.5) |

Note: % = n/N × 100. A TEAE that had a start date that occurred during a certain Treatment Period is regarded as TEAE at that Treatment Period. Any TEAEs that lasted across treatment periods are only counted once in the treatment period the event started. If a participant had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT. Highest relationship for each patient per SOC/PT is summarized. SOCs are sorted alphabetically, and PTs are sorted by decreasing percent based on Total column. SOCs and PTs were coded using MedDRA version 25.1.
Abbreviations: N = number of participants; n = number of participants in each category; PT = Preferred Term; SOC = System Organ Class; TEAE= treatment-emergent adverse event

Pooled studies

There was no increase in incidence of related TEAEs with increasing dose in the *PNH Add-on Population*. There seems to be a higher incidence of related TEAEs while participants were on 100 mg tid (30.8% of participants) than when participants were on 150 or 200 mg tid (18.8% and 7.7%, respectively) (data cutoff 31 Mar 2023).

The type of reported events considered by the Investigator as related to the study intervention was similar across the different populations.

**TEAEs of Special Interest (AESIs)**

Meningococcal infections were considered AESIs due to the mechanism of action of danicopan and due to being administered as add-on therapy to a C5 inhibitor where this is an identified risk. Liver enzyme elevations were considered AESIs based on toxicology data in dogs and on ALT and AST elevations observed in 2 healthy volunteers after completion of treatment in a MAD study at the highest dose cohorts (ACH471-002).

*Meningococcal infections:* There were no reports of meningococcal infections in the TP1 study ALXN2040-PNH-301, neither AESIs in any of the pooled population groups.

*Liver enzyme elevations:* In TP1 study ALXN2040-PNH-301 data cutoff date of 31 Mar 2023, 8 (14.0%) participants in the add-on danicopan group experienced TEAEs associated with liver abnormalities and 3 (10.3%) participants in the placebo group. These events included hepatic function abnormal, liver disorder, ALT increased, AST increased, blood bilirubin increased, and hepatic enzyme increased. Two of these participants met the protocol-specified stopping criteria related to liver enzymes elevation. One serious AESI of blood bilirubin increased experienced by a participant in the add-on danicopan group was assessed as related to study intervention and led to treatment discontinuation. In TP2, there were 6 nonserious AESIs in 6 (7.3%) participants related to liver abnormalities and in LTE, there were 2 (2.5%) participants' related liver abnormalities. None met Hy's Law criteria. The incidence of liver enzyme elevations decreased with longer treatment duration.

The AESIs associated with liver abnormalities up to the clinical database cutoff date of 31 Mar 2023 are summarized in Table below.

**Table 92: Treatment-Emergent Adverse Events of Special Interest: Liver Enzyme Elevations Up to the Clinical Database Cutoff Date of 31 Mar 2023 (Combined PNH and C3G/IC-MPGN Population)**

| System Organ Class<br>Preferred term | PNH Add-on (N = 96) | | PNH Monotherapy (N = 10) | | All PNH (N = 106) | | C3G/IC-MPGN (N = 37) | | Combined PNH and C3G/ IC-MPGN (N = 143) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| Total patient-years | NA | 141.5 | NA | 21.9 | NA | 163.4 | NA | 48.4 | NA | 211.7 |
| Participants with at least 1 TEAE of liver enzyme elevation | 19[a] (19.8) | 34 (24.0) | 1 (10.0) | 3 (13.7) | 20[a] (18.9) | 37 (22.6) | 3 (8.1) | 5 (10.3) | 23[a] (16.1) | 42 (19.8) |
| Investigations | 12 (12.5) | 25 (17.7) | 1 (10.0) | 3 (13.7) | 13 (12.3) | 28 (17.1) | 3 (8.1) | 5 (10.3) | 16 (11.2) | 33 (15.6) |
| Alanine aminotransferase increased | 6 (6.3) | 7 (4.9) | 1 (10.0) | 2 (9.1) | 7 (6.6) | 9 (5.5) | 1 (2.7) | 1 (2.1) | 8 (5.6) | 10 (4.7) |
| Aspartate aminotransferase increased | 4 (4.2) | 4 (2.8) | 1 (10.0) | 1 (4.6) | 5 (4.7) | 5 (3.1) | 2 (5.4) | 2 (4.1) | 7 (4.9) | 7 (3.3) |
| Blood bilirubin increased | 3 (3.1) | 12 (8.5) | 0 | 0 | 3 (2.8) | 12 (7.3) | 0 | 0 | 3 (2.1) | 12 (5.7) |
| Hepatic enzyme increased | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 1 (2.7) | 1 (2.1) | 2 (1.4) | 2 (0.9) |
| Transaminases increased | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 1 (2.7) | 1 (2.1) | 2 (1.4) | 2 (0.9) |
| Hepatobiliary disorders | 8 (8.3) | 9 (6.4) | 0 | 0 | 8 (7.5) | 9 (5.5) | 0 | 0 | 8 (5.6) | 9 (4.3) |
| Hepatic function abnormal | 3 (3.1) | 3 (2.1) | 0 | 0 | 3 (2.8) | 3 (1.8) | 0 | 0 | 3 (2.1) | 3 (1.4) |
| Hyperbilirubinaemia | 3 (3.1) | 4 (2.8) | 0 | 0 | 3 (2.8) | 4 (2.4) | 0 | 0 | 3 (2.1) | 4 (1.9) |
| Liver disorder | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Portal vein dilatation | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |

Note: Liver enzyme elevation were identified using 2 Standardized MedDRA Queries (SMQs) narrow: SMQ Drug related hepatic disorders - severe events only [narrow] [20000007], and SMQ Liver related investigations, signs and symptoms [narrow] [20000008].
Percentages are based on the total number of participants in each column.
Rate of AEs is adjusted by patient-years of exposure, defined as (number of events)/100 patient-years.
Treatment-emergent AEs are AEs with a start date and start time on or after the date and time of the first dose, and within 30 days of the last dose of danicopan.
Under participant count columns, n (%), if a participant had more than 1 event for a particular SOC, the participant is counted only once for that SOC under n (%). If a participant had more than 1 event for a particular PT, the participant is counted only once for that PT.
AEs were coded using MedDRA Version 25.1.
[a] One participant was included in the analysis of the initial submission, but not in the analyses at this Summary of Clinical Safety Addendum because this participant experienced an AE that occurred before the first dose of study drug.
Abbreviations: AE = adverse event; C3G = complement 3 glomerulopathy; E = number of events; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

### TEAEs of haemolysis in participants with PNH

In the PNH development programme, events of breakthrough haemolysis (BTH) were not reported following protocol-specified criteria but were reported as TEAEs according to the Investigator's judgement of what constitutes BTH. Hence, TEAEs of haemolysis in addition to BTH were collectively reviewed.

In Study ALXN2040-PNH-301, 14 TEAEs of haemolysis (8 haemolysis and 6 BTH) were reported in 10 participants (data cutoff 31 Mar 2023). None of these events had LDH above 2.2 × ULN; none led to discontinuation of treatment. In TP1, 2 TEAEs of haemolysis were reported in 2 participants (all on stable ravulizumab treatment). None of these events had LDH above 1.5 × ULN (upper limit of normal); none led to discontinuation of treatment, nonserious BTH.

In the PNH Add-on Population, there were 16 TEAEs of haemolysis (9 events of haemolysis and 7 of BTH) reported in 12 participants based on the clinical judgement of the Investigator, and none of the events led to discontinuation of study treatment. At or near the time of the events, LDH values were not higher than 2.2 × ULN. Four participants were on stable eculizumab (2 participants in Study ACH471-101 and 2 participants in Study ALXN2040 PNH-301) and 8 on ravulizumab (8 participants in Study ALXN2040 PNH-301) treatment.

In the All PNH Population, there were 26 events of haemolysis (11 events of haemolysis and 15 events of BTH) in 17 participants (Data cut 31Mar2023) based on the clinical judgement of the Investigator. This includes 10 TEAEs of haemolysis (2 events of haemolysis and 8 of breakthrough haemolysis) in 5 participants from the PNH Monotherapy Population. None of the events led to discontinuation of treatment.

### *2.6.8.3. Serious adverse event/deaths/other significant events*

***Serious adverse events***

Phase 3 PNH Study ALXN2040-PNH-301

In TP1 data cutoff 31 Mar 2023, there were 3 (5.3%) participants in the danicopan and 2 (6.9%) in the placebo group who experienced at least 1 SAE. There was one (2.0%) event of severe cholecystitis in the danicopan arm. Two SAEs (pancreatitis and blood bilirubin increased) in the same participant in the danicopan group were considered by the Investigator as related to study intervention and led to study discontinuation. However, the Sponsor considered the SAEs of pancreatitis and blood bilirubin increased reported do not constitute ADRs as this clinical presentation, those appears consistent with complications of underlying disease. Twelve additional SAEs were reported in 7 participants who were all from Study ALXN2040-PNH-301 in the Safety Database from ongoing PNH studies as of 01 Oct 2022.

The serious TEAEs during Treatment Period 1 is summarized in Table below

**Table 93: Summary of Serious TEAEs During Treatment Period 1 (Study ALXN2040-PNH-301, Safety Analysis Set) (Data cutoff 31 Mar 2023)**

| System Organ Class<br>Preferred Term | Danicopan<br>N = 57 | | Placebo<br>N = 29 | |
|---|---|---|---|---|
| | n% | E | n% | E |
| Any SAE | 3 (5.3) | 5 | 2 (6.9) | 4 |
| Blood and lymphatic system disorders | 0 | 0 | 1 (3.4) | 1 |
| Anaemia | 0 | 0 | 1 (3.4) | 1 |
| Gastrointestinal disorders | 1 (1.8) | 1 | 1 (3.4) | 1 |
| Pancreatitis | 1 (1.8) | 1 | 0 | 0 |
| Abdominal pain | 0 | 0 | 1 (3.4) | 1 |
| Hepatobiliary disorders | 2 (3.5) | 2 | 0 | 0 |
| Cholecystitis | 1 (1.8) | 1 | 0 | 0 |
| Cholelithiasis | 1 (1.8) | 1 | 0 | 0 |
| Infections and infestations | 1 (1.8) | 1 | 0 | 0 |
| COVID-19 | 1 (1.8) | 1 | 0 | 0 |
| Investigations | 1 (1.8) | 1 | 0 | 0 |

| System Organ Class<br>Preferred Term | Danicopan<br>N = 57 | | Placebo<br>N = 29 | |
|---|---|---|---|---|
| | n% | E | n% | E |
| Blood bilirubin increased | 1 (1.8) | 1 | 0 | 0 |
| Nervous system disorders | 0 | 0 | 1 (3.4) | 2 |
| Headache | 0 | 0 | 1 (3.4) | 2 |

Note: In summarizing n (%), if a participant had multiple events for a particular SOC or Preferred Term, they were counted only once for that SOC or Preferred Term. SOCs are sorted alphabetically, and Preferred Terms are sorted by decreasing percent based on the danicopan column. SOCs and Preferred Terms were coded using MedDRA Version 25.1.
Abbreviations: COVID-19 = coronavirus disease 2019; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Pooled Studies

The SAE profile was similar between the All PNH Population, the PNH Add-on Population and Combined PNH and C3G/IC-MPGN Population (Table below). In the All PNH Population, 28.3% of participants reported at least 1 SAE.

**Table 94: Serious Treatment-Emergent Adverse Events (Combined PNH and C3G/IC-MPGN Population) (Data cutoff 31 Mar 2023)**

| System Organ Class<br>Preferred term | PNH Add-on (N = 96) | | PNH Monotherapy (N = 10) | | All PNH (N = 106) | | C3G/ IC-MPGN (N = 37) | | Combined PNH and C3G/ IC-MPGN (N = 143) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| Total patient-years | NA | 141.5 | NA | 21.9 | NA | 163.4 | NA | 48.4 | NA | 211.7 |
| Participants with at least 1 serious TEAE | 26 (27.1) | 49 (34.6) | 4 (40.0) | 8 (36.6) | 30 (28.3) | 57 (34.9) | 5 (13.5) | 6 (12.4) | 35 (24.5) | 63 (29.8) |
| Infections and infestations | 10 (10.4) | 13 (9.2) | 3 (30.0) | 3 (13.7) | 13 (12.3) | 16 (9.8) | 1 (2.7) | 1 (2.1) | 14 (9.8) | 17 (8.0) |
| COVID-19 | 4 (4.2) | 4 (2.8) | 0 | 0 | 4 (3.8) | 4 (2.4) | 0 | 0 | 4 (2.8) | 4 (1.9) |
| Cystitis | 1 (1.0) | 1 (0.7) | 1 (10.0) | 1 (4.6) | 2 (1.9) | 2 (1.2) | 0 | 0 | 2 (1.4) | 2 (0.9) |
| Pneumonia | 2 (2.1) | 2 (1.4) | 0 | 0 | 2 (1.9) | 2 (1.2) | 0 | 0 | 2 (1.4) | 2 (0.9) |
| COVID-19 pneumonia | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Device related infection | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Gastroenteritis | 0 | 0 | 1 (10.0) | 1 (4.6) | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Infectious mononucleosis | 0 | 0 | 1 (10.0) | 1 (4.6) | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Neutropenic sepsis | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Pyelonephritis | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Rhinovirus infection | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7) | 1 (2.1) | 1 (0.7) | 1 (0.5) |
| Staphylococcal sepsis | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Tracheobronchitis viral | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Blood and lymphatic system disorders | 5 (5.2) | 5 (3.5) | 2 (20.0) | 2 (9.1) | 7 (6.6) | 7 (4.3) | 0 | 0 | 7 (4.9) | 7 (3.3) |
| Breakthrough haemolysis | 1 (1.0) | 1 (0.7) | 2 (20.0) | 2 (9.1) | 3 (2.8) | 3 (1.8) | 0 | 0 | 3 (2.1) | 3 (1.4) |
| Haemolysis | 2 (2.1) | 2 (1.4) | 0 | 0 | 2 (1.9) | 2 (1.2) | 0 | 0 | 2 (1.4) | 2 (0.9) |
| Febrile neutropenia | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Haemorrhagic diathesis | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| General disorders and administration site conditions | 5 (5.2) | 7 (4.9) | 1 (10.0) | 1 (4.6) | 6 (5.7) | 8 (4.9) | 1 (2.7) | 1 (2.1) | 7 (4.9) | 9 (4.3) |
| Pyrexia | 3 (3.1) | 4 (2.8) | 1 (10.0) | 1 (4.6) | 4 (3.8) | 5 (3.1) | 1 (2.7) | 1 (2.1) | 5 (3.5) | 6 (2.8) |
| Disease progression | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Influenza like illness | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Stent-graft endoleak | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Gastrointestinal disorders | 4 (4.2) | 5 (3.5) | 0 | 0 | 4 (3.8) | 5 (3.1) | 0 | 0 | 4 (2.8) | 5 (2.4) |
| Pancreatitis | 2 (2.1) | 2 (1.4) | 0 | 0 | 2 (1.9) | 2 (1.2) | 0 | 0 | 2 (1.4) | 2 (0.9) |
| Abdominal pain upper | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Diarrhoea | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Dieulafoys vascular malformation | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Investigations | 3 (3.1) | 4 (2.8) | 1 (10.0) | 2 (9.1) | 4 (3.8) | 6 (3.7) | 0 | 0 | 4 (2.8) | 6 (2.8) |
| Alanine aminotransferase increased | 0 | 0 | 1 (10.0) | 1 (4.6) | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Aspartate aminotransferase increased | 0 | 0 | 1 (10.0) | 1 (4.6) | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Blood bilirubin increased | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Body temperature increased | 1 (1.0) | 2 (1.4) | 0 | 0 | 1 (0.9) | 2 (1.2) | 0 | 0 | 1 (0.7) | 2 (0.9) |
| Haemoglobin decreased | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Hepatobiliary disorders | 3 (3.1) | 4 (2.8) | 0 | 0 | 3 (2.8) | 4 (2.4) | 0 | 0 | 3 (2.1) | 4 (1.9) |
| Cholecystitis | 2 (2.1) | 3 (2.1) | 0 | 0 | 2 (1.9) | 3 (1.8) | 0 | 0 | 2 (1.4) | 3 (1.4) |
| Cholelithiasis | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |

| System Organ Class<br>Preferred term | PNH Add-on (N = 96) | | PNH Monotherapy (N = 10) | | All PNH (N = 106) | | C3G/ IC-MPGN (N = 37) | | Combined PNH and C3G/ IC-MPGN (N = 143) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Renal and urinary disorders | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 2 (5.4) | 2 (4.1) | 3 (2.1) | 3 (1.4) |
| Acute kidney injury | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7) | 1 (2.1) | 1 (0.7) | 1 (0.5) |
| Haemoglobinuria | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Renal impairment | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7) | 1 (2.1) | 1 (0.7) | 1 (0.5) |
| Cardiac disorders | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 1 (2.7) | 1 (2.1) | 2 (1.4) | 2 (0.9) |
| Atrial fibrillation | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7) | 1 (2.1) | 1 (0.7) | 1 (0.5) |
| Pericardial effusion | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Neoplasms benign, malignant, and unspecified (incl cysts and polyps) | 2 (2.1) | 2 (1.4) | 0 | 0 | 2 (1.9) | 2 (1.2) | 0 | 0 | 2 (1.4) | 2 (0.9) |
| Invasive ductal breast carcinoma | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Schwannoma | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Nervous system disorders | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 1 (2.7) | 1 (2.1) | 2 (1.4) | 2 (0.9) |
| Headache | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Presyncope | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7) | 1 (2.1) | 1 (0.7) | 1 (0.5) |
| Respiratory, thoracic, and mediastinal disorders | 2 (2.1) | 3 (2.1) | 0 | 0 | 2 (1.9) | 3 (1.8) | 0 | 0 | 2 (1.4) | 3 (1.4) |
| Pulmonary embolism | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Pulmonary haemorrhage | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Pulmonary oedema | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Ear and labyrinth disorders | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Vertigo | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Injury, poisoning and procedural complications | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Femur fracture | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Musculoskeletal and connective tissue disorders | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Arthralgia | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |

Note: Percentages are based on the total number of participants in each column.
Rate of AEs is adjusted by patient-years of exposure, defined as (number of events)/100 patient-years.
Treatment-emergent AEs are AEs with a start date and start time on or after the date and time of the first dose of danicopan.
Under participant count columns, n (%), if a participant had more than 1 event for a particular SOC, the participant is counted only once for that SOC under n (%). If a participant had more than 1 event for a particular PT, the participant is counted only once for that PT.
AEs were coded using MedDRA Version 25.1.
Abbreviations: AE = adverse event; C3G = complement 3 glomerulopathy; COVID-19 = coronavirus disease 2019; E = number of events; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Non-pooled studies

Study ALXN2040-PNH-303 is conducted in participants with PNH. As of 30 Jun 2023, 51 participants have enrolled in the ongoing Study ALXN2040-PNH-303, to date, 1 SAE has been reported in 1 participant

Study ALXN2040-GA-201 is an ongoing blinded Phase 2 study conducted in participants with GA. As of 30 Jun 2023, 364 participants were enrolled in an ongoing blinded Phase 2 Study ALXN2040-GA-201, to date 28 SAEs were reported in 21 participants, of which 1 was fatal, considered by the Investigator as not related to study intervention.

***Deaths***

There were no related deaths to danicopan treatment in the pivotal study ALXN2040-PNH-301, neither in participants with PNH and C3G/IC-MPGN in pooled analysis studies, and nor in clinical pharmacology studies.

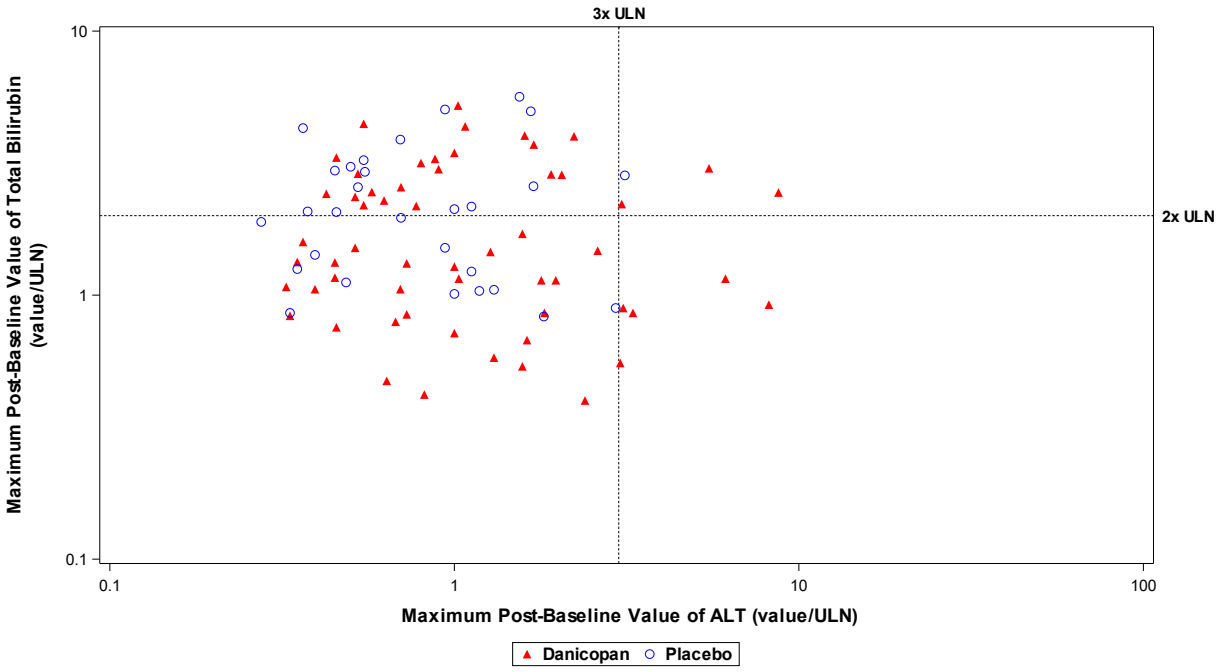
As of the cutoff date of 30 Jun 2023, 1 participant in Study ALXN2040 PNH 301 experienced an SAE of pneumonia and died. Treatment with danicopan was ongoing at the time of death, and the Investigator assessed the event as unrelated to danicopan treatment.

### *2.6.8.4. Laboratory findings*

Phase 3 PNH Study: ALXN2040-PNH-301

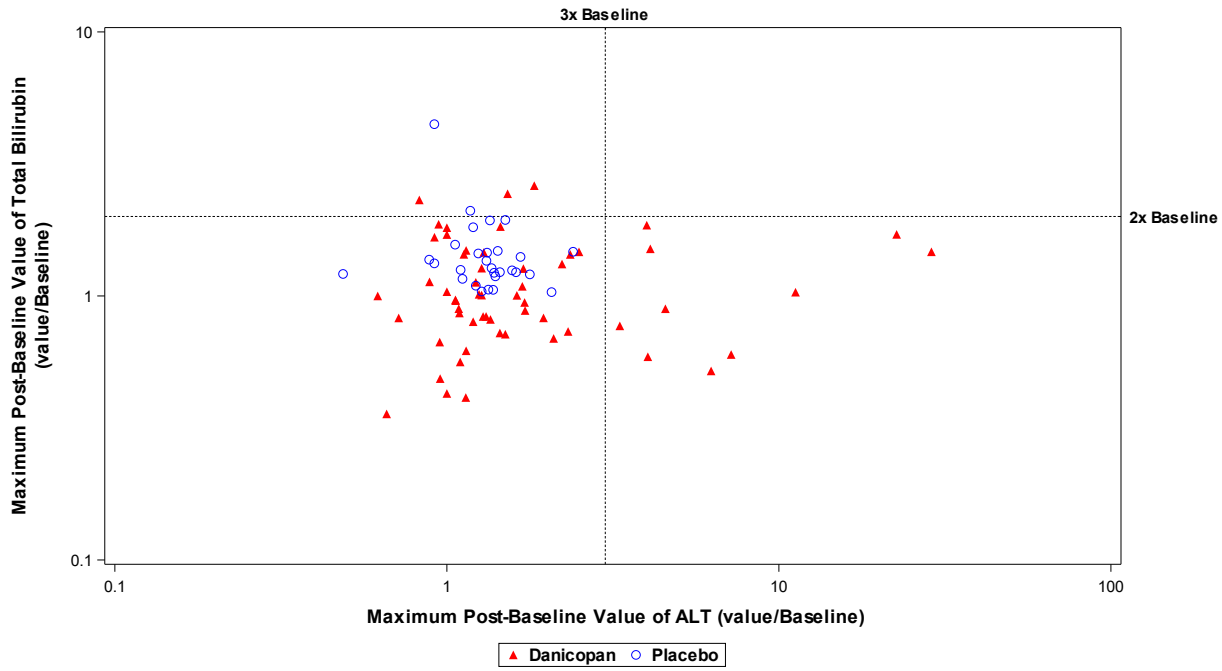
As of the cutoff date of 31 Mar 2023, following postbaseline elevations in ALT were observed during TP1: a higher incidence of ALT elevations was reported in the danicopan group (n = 8; 14.0%) compared with placebo group (n = 1; 3.4%), 8 participants in the add-on danicopan group had ALT > 3 × ULN as the highest post-Baseline value (5 participants had ALT > 3 × ULN and ≤ 5 × ULN, 1 participant had ALT > 5 × ULN and ≤ 8 ×ULN, and 2 participants had ALT > 8 × ULN). There was 1 participant in the add-on danicopan group with ALT > 3 × ULN and total bilirubin > 2 × ULN. One participant had total bilirubin values of 2.5 × ULN at Baseline that decreased after initiation of treatment. There was no TEAE reported. These laboratory findings were not considered as confirmed Hy's Law cases as the participants either had these abnormalities present at Baseline or had other possible etiologies (eg, haemolysis).

Additional safety analyses using ALT and total bilirubin data were performed to assess for drug induced serious hepatoxicity (DISH). Evaluation of drug-induced serious hepatotoxicity (eDISH) plots of peak bilirubin values versus peak ALT values and baseline-corrected modified drug-induced serious hepatotoxicity (mDISH) for the danicopan group and placebo group for TP1 as of the Clinical Database cutoff date of 31 Mar 2023 are provided in Figures below.




Note: Baseline is defined as the last nonmissing value prior to the first dose of study intervention.
Abbreviations: ALT = alanine aminotransferase; eDISH = evaluation of drug-induced serious hepatotoxicity; TP1 = Treatment Period 1; ULN = upper limit of normal

**Figure 39: eDISH Scatter Plot of Maximum Total Bilirubin Versus Maximum ALT During TP1 (Study ALXN2040-PNH-301, Interim Safety Analysis Set)**




Note: Baseline is defined as the last nonmissing value prior to the first dose of study intervention. mDISH: modified eDISH plot with maximum total bilirubin and maximum ALT expressed in multiples of Baseline values.
Abbreviations: ALT = alanine aminotransferase; eDISH = evaluation of drug-induced serious hepatotoxicity; TP1 = Treatment Period 1

**Figure 40: mDISH Scatter Plot of Maximum Total Bilirubin Versus Maximum ALT During TP1 (Study ALXN2040-PNH-301, Interim Safety Analysis Set)**

At the initial submission (28 Jun 2022), the TP1 eDISH plot showed 3 participants in the right upper quadrant, 2 from the add-on danicopan group and 1 from the placebo group. None of these laboratory abnormalities were considered as confirmed Hy's Law cases. As of the cutoff date 31 Mar 2023, the eDISH plot showed 1 additional participant in the right upper quadrant (**Figure 39**), this participant in the add-on danicopan group had ALT increase to 3.4 × ULN and AST increase to 2.1 × ULN at Week 6; total bilirubin was 1.5 × ULN and ALP 1.0 × ULN, and was diagnosed with pancreatitis. The participant also had the serious TEAE of blood bilirubin increased. These laboratory findings were not considered as confirmed Hy's Law cases. After correction for Baseline values, the mDISH plot showed no participants from either treatment group in the right upper quadrant, further indicating these abnormalities were present since Baseline for which these were not considered as confirmed Hy's Law cases (**Figure 40**).

Pooled studies

Laboratory abnormalities were similar across the populations. Most of the chemistry, haematology, and coagulation abnormalities were not clinically meaningful.

Liver enzyme abnormality thresholds relative to ULN values are summarized by population in Table below. None of the abnormalities were considered as confirmed Hy's Law cases.

One participant from the PNH Monotherapy Population had an increase in ALT of > 8 × ULN and experienced an SAE of ALT and AST increased concurrent with a serious event of BTH.

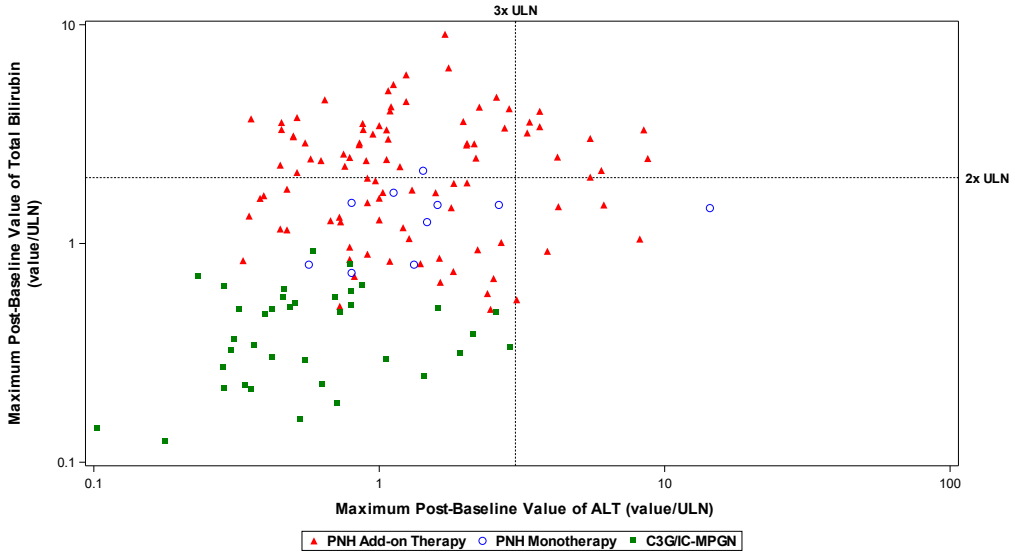
None of the abnormalities were considered as confirmed Hy's Law cases due to presenting with high ALT Baseline values and total bilirubin values remaining < 2 × the participant's Baseline at the time of peak in ALT in the Combined PNH and C3G/IC-MPGN Population. In addition, participants also had increased LDH levels suggestive of haemolysis.

**Table 95: Summary of Liver Enzyme Elevations (Combined PNH and C3G/IC-MPGN Population). Cutoff Date 31 Mar 2023**

| Variable | PNH Add-on (N = 96) | PNH Monotherapy (N = 10) | All PNH (N = 106) | C3G/IC-MPGN (N = 37) | Combined PNH and C3G/IC-MPGN (N = 143) |
|---|---|---|---|---|---|
| Alanine aminotransferase, n (%) [E] | | | | | |
| > 3 × ULN | 15 (15.6) [36] | 1 (10.0) [2] | 16 (15.1) [38] | 0 | 16 (11.2) [38] |
| > 5 × ULN | 7 (7.3) [13] | 1 (10.0) [1] | 8 (7.5) [14] | 0 | 8 (5.6) [14] |
| > 8 × ULN | 3 (3.1) [3] | 1 (10.0) [1] | 4 (3.8) [4] | 0 | 4 (2.8) [4] |
| Aspartate aminotransferase, n (%) [E] | | | | | |
| > 3 × ULN | 6 (6.3) [10] | 4 (40.0) [8] | 10 (9.4) [18] | 2 (5.4) [3] | 12 (8.4) [21] |
| > 5 × ULN | 1 (1.0) [2] | 2 (20.0) [3] | 3 (2.8) [5] | 1 (2.7) [1] | 4 (2.8) [6] |
| > 8 × ULN | 0 | 1 (10.0) [2] | 1 (0.9) [2] | 1 (2.7) [1] | 2 (1.4) [3] |
| Alanine aminotransferase > 3 × ULN and total bilirubin > 2 × ULN, n (%) [E] | 4 (4.2) [8] | 0 | 4 (3.8) [8] | 0 | 4 (2.8) [8] |
| Alanine aminotransferase > 3 × ULN, total bilirubin > 2 × ULN, and alkaline phosphatase < 2 × ULN, n (%) [E] | 3 (3.1) [4] | 0 | 3 (2.8) [4] | 0 | 3 (2.1) [4] |

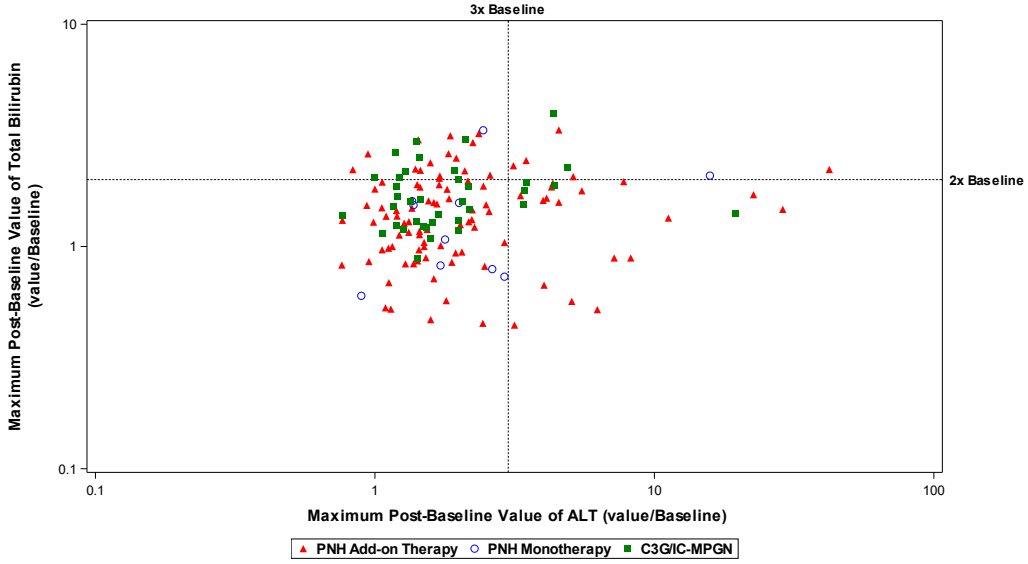
Note: Percentages are based on the total number of participants in each column.
Abbreviations: C3G = complement 3 glomerulopathy; E = the number of a specific laboratory results; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; N = number of participants; n = the number of participants with a specific laboratory result; PNH = paroxysmal nocturnal hemoglobinuria; ULN = upper limit of normal

Additional safety analyses using ALT and total bilirubin data were performed to assess for DISH. Evaluation of eDISH and mDISH plots of peak bilirubin values versus peak ALT values for the Combined PNH and C3G/IC-MPGN Population is provided in Figures below.




Note: Baseline is defined as the last nonmissing value prior to the first dose of danicopan.
Abbreviations: ALT = alanine aminotransferase; C3G = complement 3 glomerulopathy; eDISH = evaluation of drug-induced serious hepatotoxicity; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; PNH = paroxysmal nocturnal hemoglobinuria; ULN = upper limit of normal

**Figure 41: eDISH Scatter Plot of Maximum Total Bilirubin Versus Maximum ALT Up to the Clinical Database Cutoff Date of 31 Mar 2023 (Combined PNH and C3G/IC-MPGN Population)**




Note: Baseline is defined as the last nonmissing value prior to the first dose of danicopan.
Abbreviations: ALT = alanine aminotransferase; C3G = complement 3 glomerulopathy; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; mDISH = baseline-corrected modified drug-induced serious hepatotoxicity; PNH = paroxysmal nocturnal hemoglobinuria

**Figure 42: mDISH Scatter Plot of Maximum Total Bilirubin Versus Maximum ALT Up to the Clinical Database Cutoff Date of 31 Mar 2023 (Combined PNH and C3G/IC-MPGN Population)**

The eDISH plot (Figure 39) showed 10 participants in the right upper quadrant, which are 2 additional participants since the initial submission. All participants in the quadrant are from the PNH Add-on Population. Nine participants are from Study ALXN2040 PNH 301 and 1 participant is from Study ACH471 101. None of these laboratory abnormalities were confirmed Hy's Law cases. After correction

for Baseline values, the mDISH plot (Figure 40) showed 8 participants in the right upper quadrant as of the Clinical Database cutoff date; 5 from the PNH Add-on Population, 1 from the PNH Monotherapy Population, and 2 from the C3G/IC-MPGN Population. These are 3 additional participants (all from the PNH Add-on Population) compared with the initial submission.

Overall, ALT elevations observed in the PNH Add-on Population were > 3 × ULN, and resolved while on danicopan treatment. In addition, total bilirubin was < 2 × Baseline value at the time of peak in ALT. Other ALT elevations observed in the PNH Add-on Population and PNH Monotherapy Population occurred in context of BTH or cholecystitis. ALT elevations observed in the C3G/IC-MPGN Population were > 2 × Baseline value, but < 3 × ULN in eDISH. Therefore, these were not considered confirmed Hy's Law cases as there were other factors contributing to these laboratory abnormalities.

For the generation of the eDISH and mDISH plots, the Applicant used any ALT ≥ 3 × ULN and any total bilirubin ≥ 2 × ULN as search criteria, since ALT has greater liver tissue specificity than AST.

Using the alternative criteria defined as any post-baseline total bilirubin elevation to ≥ 2 × ULN occurring on or within 30 days after a post-baseline ALT or AST elevation to ≥ 3 × ULN and concurrent ALP is < 2 × ULN, there were 6 potential Hy's law cases (right upper quadrant) in the PNH Add-on Population and 1 in the PNH Monotherapy Population. Upon review of these cases none were considered confirmed Hy's Law cases, as the liver enzyme abnormalities were consistent with underlying disease or had alternative aetiology (eg, pancreatitis).

Using the criteria defined as any post-baseline total bilirubin elevation to ≥ 2 × ULN with no or minimal hepatocellular injury (ALT and AST < 3 × ULN) to identify cholestasis cases, 42 cholestasis cases were identified for further assessment in the PNH Add-on Population. Of the 42 cases identified in the Cholestasis quadrant, 6 cases were from Study ACH471-101 and 36 cases were from Study ALXN2040-PNH-301. Cases appearing in this quadrant represent those with total bilirubin ≥ 2 × ULN without any increase in ALT or AST. Upon review, none of these elevations corresponded to clinical events of cholestasis and most cases did not have elevations in ALP. Additionally, there was no meaningful increase of total bilirubin from baseline. In many cases, total bilirubin values were above ULN at screening and/or baseline, and elevations in total bilirubin were driven by increases in indirect bilirubin. Most elevations resolved during treatment with danicopan. None of these cases were considered indicative of injury, none of these cases were considered indicative of liver injury.

**Table 96: Participants in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury (DILI) Screening Plot**

| Variable | PNH Add-on[a] (N = 96) n/NW (%) | PNH Monotherapy[b] (N = 10) n/NW (%) |
|---|---|---|
| Potential Hy's law (right upper) | 6/96 ( 6.3) | 1/10 (10.0) |
| Cholestasis (left upper) | 42/96 (43.8) | 0/10 ( 0.0) |
| Temple's corollary (right lower) | 5/96 ( 5.2) | 1/10 (10.0) |
| Total | 53/96 (55.2) | 2/10 (20.0) |

Note: Potential Hy's law cases are defined as any post-baseline total bilirubin elevation to ≥ 2 × ULN occurring on or within 30 days after a post-baseline ALT or AST elevation to ≥ 3 × ULN and concurrent ALP is < 2 × ULN.
Cholestasis cases are defined as jaundice occurs (total bilirubin ≥ 2 × ULN) with no or minimal hepatocellular injury (ALT and AST less than 3 × ULN).
Temple's corollary cases are defined as ALT and/or AST ≥ 3 × ULN but there is no accompanying total bilirubin elevation or jaundice.
[a] Pooled Studies ACH471-101 + ALXN2040-PNH-301.
[b] Pooled Studies ACH471-100 + ACH471-103.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of participants in treatment arm; n = number of participants meeting criteria; NW = number of participants with data; PNH = paroxysmal nocturnal hemoglobinuria; ULN = upper limit of normal

Results obtained were consistent with those obtained in the assessment of drug-induced hepatotoxicity (DISH plots) (data cutoff 31 Mar 2023). The hepatotoxicity assessments performed identified cases in the right and left upper quadrant that upon review were not confirmed Hy's law cases or consistent with cholestasis. The laboratory abnormalities identified were either due to underlying PNH disease or had an alternative aetiology.

No clinically meaningful findings in vital signs, ECGs, and physical examinations were observed in ALXN2040-PNH-301. No pooled analysis of vital signs, physical examinations, and ECGs was performed for participants in any of the populations.

### *2.6.8.5. In vitro biomarker test for patient selection for safety*

Not applicable.

### *2.6.8.6. Safety in special populations*

As of the cutoff date of 31 Mar 2023, 8 participants were < 18 years of age, 111 participants were 18 through 64 years of age, 15 participants were 65 through 74 years of age, and 9 participants were 75 through 84 years of age. The AE profiles were generally similar across the age groups. No increase of TEAEs, related TEAEs, Grade 3 and 4 TEAEs, TEAEs leading to discontinuation of study intervention, or SAEs was observed with increasing age. The incidence of AESI (liver enzyme elevations) was higher in the 65 through 74 years and 75 through 84 years age groups (20.0% and 22.2% of participants, respectively) compared to the 18 through 64 years age group (13.5% of participants). The incidence in the < 18 years of age group was 37.5% (3/8 participants). Data on the use of danicopan in elderly patients are considered limited, especially in patients ≥ 75 years.

More female participants experienced SAEs than male participants (26.3% for female and 22.2% for male participants) and more female participants experienced SAEs considered related to the study intervention (6.3% for females and none for male participants). Other safety variables were generally similar across the sex groups.

The AE profiles were generally similar across the race groups and the geographic regions.

A single oral 200-mg dose of danicopan was well tolerated in participants with severe renal impairment (RI) and participants with normal renal function (ACH471-009). Other than expected differences in clinical laboratory parameters for participants with severe RI (ie, blood urea nitrogen and creatinine), the safety profiles between the 2 renal function groups were comparable.

A single oral 200 mg dose of danicopan was well tolerated in participants with moderate hepatic insufficiency (HI) and healthy participants (ACH471-012). There were no AEs reported in participants with HI. Studies have not been conducted in participants with severe HI, therefore, danicopan is not recommended in this patient population.

The use of danicopan in pregnant and lactating participants has not been studied.

The effect of danicopan on human fertility has not been evaluated.

#### *2.6.8.7. Immunological events*

Not applicable.

#### *2.6.8.8. Safety related to drug-drug interactions and other interactions*

See Pharmacokinetics section.

#### *2.6.8.9. Discontinuation due to adverse events*

As data cutoff 31 Mar 2023, in TP1 Phase 3 PNH Study ALXN2040-PNH-301, 4 (4.4%) participants experienced TEAEs leading to discontinuation of study intervention: 3 (5.3%) participants in the add-on danicopan group and 1 (3.4%) participant in the placebo group. Two participants (1 in the add-on danicopan group and 1 in the placebo group) discontinued due to protocol-specified stopping criteria related to abnormal liver enzyme laboratory values One participant in the add-on danicopan group was discontinued due to a nonserious TEAE related to abnormal liver enzyme laboratory values. However, this participant did not meet the stopping criteria related to abnormal liver enzyme laboratory values. One additional participant in the add-on danicopan group discontinued treatment due to TEAEs during TP1. This participant has serious TEAEs of blood bilirubin increased and pancreatitis considered by the investigator as related to study intervention, however, the Sponsor considered the SAEs of pancreatitis and blood bilirubin increased reported do not constitute ADRs as those appears consistent with complications of underlying disease. In TP2, there were no TEAEs leading to treatment discontinuation in the add-on danicopan group versus 1 (3.7%) participant in the placebo group.

As of the clinical database cutoff date, there were no discontinuations due to haemolysis.

For the studies in participants with PNH treated with danicopan monotherapy and in participants with C3G/IC-MPGN, instead of TEAEs leading to study treatment discontinuation, only TEAEs leading to study discontinuation were recorded.

**Table 97: Treatment-Emergent Adverse Events Leading to Study Treatment or Study Discontinuation Up to the Clinical Database Cutoff Date of 31 Mar 2023 (Combined PNH and C3G/IC-MPGN Population)**

| System Organ Class<br>Preferred term | PNH Add-on (N = 96) | | PNH Monotherapy (N = 10) | | All PNH (N = 106) | | C3G/IC-MPGN (N = 37) | | Combined PNH and C3G/ IC-MPGN (N = 143) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) | n (%) | E (Rate) |
| Total patient-years | NA | 141.5 | NA | 21.9 | NA | 163.4 | NA | 48.4 | NA | 211.7 |
| Participants with at least 1 TEAE | 6 (6.3) | 8 (5.7) | 1 (10.0) | 3 (13.7) | 7 (6.6) | 11 (6.7) | 2 (5.4) | 2 (4.1) | 9 (6.3) | 13 (6.1) |
| Investigations | 3 (3.1) | 4 (2.8) | 1 (10.0) | 2 (9.1) | 4 (3.8) | 6 (3.7) | 1 (2.7) | 1 (2.1) | 5 (3.5) | 7 (3.3) |
| Alanine aminotransferase increased | 1 (1.0) | 1 (0.7) | 1 (10.0) | 1 (4.6) | 2 (1.9) | 2 (1.2) | 0 | 0 | 2 (1.4) | 2 (0.9) |
| Aspartate aminotransferase increased | 1 (1.0) | 1 (0.7) | 1 (10.0) | 1 (4.6) | 2 (1.9) | 2 (1.2) | 0 | 0 | 2 (1.4) | 2 (0.9) |
| Blood bilirubin increased | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Blood creatine phosphokinase increased | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7) | 1 (2.1) | 1 (0.7) | 1 (0.5) |
| Hepatic enzyme increased | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Hepatobiliary disorders | 2 (2.1) | 2 (1.4) | 0 | 0 | 2 (1.9) | 2 (1.2) | 0 | 0 | 2 (1.4) | 2 (0.9) |
| Cholecystitis | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Hepatic function abnormal | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Blood and lymphatic system disorders | 0 | 0 | 1 (10.0) | 1 (4.6) | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Breakthrough haemolysis | 0 | 0 | 1 (10.0) | 1 (4.6) | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Gastrointestinal disorders | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Pancreatitis | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Renal and urinary disorders | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7) | 1 (2.1) | 1 (0.7) | 1 (0.5) |
| Acute kidney injury | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7) | 1 (2.1) | 1 (0.7) | 1 (0.5) |
| Respiratory, thoracic, and mediastinal disorders | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |
| Pulmonary oedema | 1 (1.0) | 1 (0.7) | 0 | 0 | 1 (0.9) | 1 (0.6) | 0 | 0 | 1 (0.7) | 1 (0.5) |

Note: Percentages are based on the total number of participants in each column.
Rate of AEs is adjusted by patient-years of exposure, defined as (number of events)/100 patient-years.
Treatment-emergent AEs are AEs with a start date and start time on or after the date and time of the first dose of danicopan.
Under participant count columns, n (%), if a participant had more than 1 event for a particular SOC, the participant is counted only once for that SOC under n (%). If a participant had more than 1 event for a particular PT, the participant is counted only once for that PT.
AEs were coded using MedDRA Version 25.1.
Abbreviations: AE = adverse event; C3G = complement 3 glomerulopathy; E = number of events; IC-MPGN = immune-complex membranoproliferative glomerulonephritis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of participants in each category; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

### *2.6.8.10. Post marketing experience*

Not applicable.

## 2.6.9. Discussion on clinical safety

The safety evaluation supporting the use of danicopan as an add-on to ravulizumab or eculizumab for the treatment of patients with PNH is mainly based on **Study ALXN2040-PNH-301**, and a pooled safety analyses of 4 studies in participants with PNH (study ACH471 101, study ALXN2040-PNH-301, Studies ACH471-100 and ACH471-103) and three studies with danicopan as monotherapy in participants with C3G/ IC MPGN.

In total, 143 subjects have been exposed to systemic danicopan. A total of 106 participants with PNH have been exposed to danicopan. Of these, 86 were evaluated in the pivotal Phase 3 Study ALXN2040-PNH-301. The pivotal study ALXN2040-PNH-301 is ongoing and data provided are based on data cutoff date of 31 Mar 2023.

*Exposure*

During TP1 Phase 3 Study ALXN2040-PNH-301, 57 participants received danicopan, and 29 participants received placebo. The median (range) exposure to danicopan was 84.0 (44.0 to 88.0) days. During the entire study through the data cutoff date, 84 participants received danicopan. Two participants in the placebo group discontinued the study during TP1 and did not receive danicopan. The overall median (range) exposure to danicopan was 427.5 (44.0 to 769.0) days

Most part of PNH patient in the ALXN2040-PNH-301 study received the 150 mg dose. Median treatment duration was the highest among patients with 150 mg dose (mean exposure to the 150 mg tid dose was 71.6 days). As of the cutoff date 31 Mar 2023, study enrollment was completed and 86 participants were randomized in a 2:1 ratio to danicopan (n = 57) or placebo (n = 29). Eighty-two participants had completed the double-blind 12-week TP1 (55 in the danicopan group and 27 in the placebo group) and entered TP2. The total patient-years for the danicopan 200 mg tid dose group was 82.7 years compared to 6.7 and 52.1 years for the danicopan 100 mg tid and 150 mg tid dose groups, respectively. Three participants who were randomized to the placebo group moved to TP2 before the 12-week TP1 was complete. Of the 82 participants who completed TP1, 80 participants completed TP2 and entered the LTE Year 1. There were no patients ongoing during TP1 and TP2. Thirty-two participants have completed Year 1 of the LTE. Two additional participants have discontinued treatment during TP1 since the initial submission, 1 due to an AE and 1 due to withdrawal by the participant.

In the PNH add-on and all PNH populations, roughly one-third of the patients was exposed to danicopan for 24-48 weeks and 26% of patients were exposed for more 48-72 weeks. These two populations are considered as the most relevant ones for the assessment of the safety of danicopan in PNH patients.

One of the limitations of the safety database is the limited number of PNH patients exposed to danicopan and the duration of exposure, particularly in this setting of a chronic indication, in addition to the absence of comparative long-term safety data.

*Adverse events*

**Study ALXN2040-PNH-301**

In the TP1 Phase-3 PNH study, the overall frequency of TEAEs was higher (75.4%) in the danicopan group than in the PBO group (62.1%). Most of events were Grade 1 or Grade 2. Grade 3 TEAEs were reported in 17.5% of participants in the add-on danicopan group compared with 13.8% in the placebo group. TEAEs of Grade 3 reported in the add-on danicopan group included: anaemia, leukopenia, neutropenia, cholecystitis, cholelithiasis, COVID-19, ALT increased, AST increased, WBC count decreased, blood pressure increased, and neutrophil count decreased. One (1.8%) participant in the

add-on danicopan group experienced a Grade 4 SAE of pancreatitis that was assessed as related to study intervention and treatment was discontinued. There were no Grade 4 TEAEs in the placebo group and no Grade 5 TEAEs in either group as of cutoff date of 31 Mar 2023.

The most frequently reported AEs by SOCs in TP1 were Gastrointestinal disorders (29.8%), Infections and infestations (19.3%), Musculoskeletal and connective tissue disorders (17.5%), Investigations (14.0%), Nervous system disorders (12.3%), and General disorders and administration site conditions (10.5%) and vascular disorders (8.8%).

In TP1, the most frequent TEAEs in the add-on danicopan group were headache (10.5%), nausea (8.8%), diarrhoea and arthralgia (7.0% each). Headache, nausea and diarrhoea were most frequently reported in placebo arm (10.3% each). The TEAEs for which the incidence was ≥ 5% higher in the add-on danicopan group compared with the placebo group, were vomiting (5.3% vs. 0%), pain in extremity (5.3% vs. 0%) and pyrexia (5.3% vs. 0%).

**PNH add-on population**

TEAEs and SAEs occurred in the PNH add-on population with remarkable higher frequencies (TEAE: 95.8%, SAE: 27.1% in the PNH Add-on population) compared to Study ALXN2040-PNH-301 (TEAE in the danicopan group: 75.4%, SAE: 5.3%). Liver enzyme elevation occurred with almost 2-fold higher frequency in the PNH Add-on population (19.8%) than in Study ALXN2040-PNH-301.

Incidence of TEAEs by danicopan dose level

Comparison of the 150 mg TID and 200 mg TID dose groups in the PNH Add-on population shows higher AE frequencies in the highest (200 mg) dose group for Any TEAE, Unrelated TEAE, Grade 1-4 TEAEs and any SAE categories when compared to the 150 mg dose group.

In the PNH Add-on Population. 92.3%, 76.8%, and 92.5% of participants reported a TEAE while on danicopan 100 mg tid, 150 mg tid, and 200 mg tid, respectively. TEAEs of special interest associated with liver enzyme elevations were experienced by 30.8%, 12.6%, and 7.5% of participants while on danicopan 100 mg tid, 150 mg tid, and 200 mg tid, respectively. SAEs were reported in 15.4%, 11.6%, and 23.9% of participants while on danicopan 100 mg tid, 150 mg tid, and 200 mg tid, respectively. One participant receiving 100 mg tid and 1 participant receiving 150 mg tid had SAEs that led to treatment or study discontinuation.

The highest AE frequencies in a given SOC were observed in the 100 mg TID group for all SOCs. For most SOCs, the AE frequency of a given SOC was lower in the 150 mg group than in the 200 mg group. AE frequencies in the 200 mg TID group were generally higher than in the 150 mg TID group, which might show some dose dependency phenomenon of AE frequencies in the PNH Add-on population.

*Related TEAEs*

In study ALXN2040-PNH-301 more related TEAEs were observed than in the PNH Add-on and All PNH studies.

Overall, the incidence of TEAEs considered related to study drug by the investigator remained higher in the add-on placebo group (27.6%) compared to the add-on danicopan group (21.1%) (data cutoff 31 Mar 2023), which was consistent with the initial submission (29.2% and 18.4%, respectively, data cutoff 28 Jun 2022). There was a slightly higher incidence of TEAEs related to liver abnormalities in the add-on danicopan group (14.0%) compared to the placebo group (10.3%).

The most frequently reported treatment-related TEAEs in the add-on danicopan group (> 3%) were nausea (7.0%), pyrexia, ALT increased, AST increased, and headache (3.5% each). Related TEAEs reported only in ≥ 2% of participants in the add-on danicopan group in TP1 were pyrexia, alanine

aminotransferase (ALT) increased, and headache. The other related events reported in ≥ 2% of participants in TP1 (nausea and aspartate aminotransferase (AST) increased) had a similar incidence between treatment groups or a higher incidence in the add-on placebo group. The only related TEAE reported in ≥ 2% of participants in the LTE was thrombocytopenia. Two related TEAEs of thrombocytopenia were reported in 2 participants. Both events were non-serious and resolved without modification to study drug, and no plausible temporal association with add-on danicopan was observed.

The Applicant selected the terms for the ADR table in the SmPC based on those that after a thorough review of the data were determined to have a causal association with danicopan. The crude ADR incidence was calculated based on the total number of add-on danicopan-treated participants using pooled data from clinical Studies ACH471-101 and ALXN2040-PNH-301, since in both studied danicopan was given as an add-on therapy to eculizumab or ravulizumab in participants with PNH. Nervous system disorders (headache), vascular disorders (hypertension), gastrointestinal disorders (vomiting), hepatobiliary disorders (hepatic enzyme increased that includes preferred terms alanine aminotransferase increased, hepatic function abnormal, hepatic enzyme increased, and transaminases increased), musculoskeletal and connective tissue disorders (pain in extremity) and general disorders and administration site conditions (pyrexia). Pyrexia, vomiting, hypertension and pain in extremity were reported at a slightly higher frequency in the danicopan arm in TP1 and are known ADRs of the background C5 inhibitors. Pyrexia and vomiting are known ADRs associated with both eculizumab and ravulizumab, hypertension and pain in extremity are known ADRs associated with eculizumab therapy. Considering the indication proposed to danicopan is as an add-on to ravulizumab or eculizumab it appears a reasonable possibility that those events were related to study treatment and have been included in section 4.8.

*AESIs*

Meningococcal infections, other possible infections and liver enzymes elevations are consider AESIs of danicopan treatment.

There were no reports of meningococcal infections and no deaths reported in study ALXN2040-PNH-301 up to the data cutoff date (31 Mar 2023).

Of note, the risk of serious infections whit danicopan treatment could not be excluded and serious infections has been included as an important potential risk in the RMP.

In TP1, 8 (14.0%) participants experienced TEAEs in the add-on danicopan group and 3 (10.3%) participants in the placebo group with events related to liver abnormalities. These events included hepatic function abnormal, liver disorder, ALT increased, AST increased, blood bilirubin increased, and hepatic enzyme increased. Two of these participants met the protocol-specified stopping criteria related to liver enzymes elevation. In TP2, there were 7 nonserious AESIs in 6 (7.3%) participants associated with liver abnormalities, and in LTE, there were 2 (2.5%) participants related liver abnormalities. The incidence of liver enzyme elevations decreased with longer treatment duration. None met Hy's Law criteria.

*SAEs*

**Study ALXN2040-PNH-301**

As of the cutoff date 31 Mar 2023, there were 3 (5.3%) participants in the danicopan and 2 (6.9%) in the placebo group who experienced at least 1 SAE in TP1. Two SAEs (pancreatitis and blood bilirubin increased) in the same participant in the danicopan group were considered by the Investigator as related to study intervention and led to study discontinuation, however, according to the Applicant those appears consistent with complications of underlying disease. The other SEA were

cholecystitis/cholelithiasis and COVID-19. In TP2, 8 (9.8%) participants had 9 SAEs; 1 SAE of headache was considered related to study intervention.

**PNH Add-on population**

As of the cutoff date 31 Mar 2023, 27.1% of participants in the PNH Add-on Population reported at least 1 SAE. The incidence of SAEs was similar between participants on 150 mg tid and 100 mg tid with an incidence of 11.6% and 15.4%, respectively. The incidence was higher (23.9%) for participants on 200 mg tid.

Six potential Hy's law cases and 42 cholestasis cases were identified in the PNH Add-on Population. Upon review of these cases none were considered confirmed Hy's Law cases, as the liver enzyme abnormalities were consistent with underlying disease or had alternative etiology (eg, pancreatitis) or were not consistent with cholestasis. The laboratory abnormalities identified either are possible due to underlying PNH disease or had an alternative etiology.

*Deaths*

As of the Clinical Database cutoff date of 31 Mar 2023, there were no deaths in any of the pooled populations and there were no deaths in Study ALXN2040-PNH-301.After the Clinical Database cutoff date, 1 participant in Study ALXN2040 PNH 301 experienced an SAE of pneumonia and died (cutoff date of 30 Jun 2023). Treatment with danicopan was ongoing at the time of death, and the Investigator assessed the event as unrelated to danicopan treatment.

*Discontinuation due to adverse events*

**Study ALXN2040-PNH-301**

A total of 4 participants, 3 (5.3%) from the add-on danicopan group and 1 (3.4%) from the add-on placebo group had TEAEs leading to treatment discontinuation in TP1. All 4 discontinuations were due to TEAEs associated with liver abnormalities. Of these participants, 3 had nonserious AESIs associated with liver abnormalities; 1 in the add-on danicopan group had serious TEAEs of blood bilirubin increased and pancreatitis considered by the investigator as related to study intervention, however, those appears consistent with complications of underlying disease. In TP2, one patient from the DAN/DAN group discontinued due to an adverse event related to liver abnormalities. There was an additional discontinuation in the LTE period of the study, due to liver enzyme elevations, which met the predefined liver enzyme-related stopping rules as well.

As of the clinical database cutoff date, there were no discontinuations due to haemolysis. Because patients may experience haemolysis which may result in increased bilirubin, AST and even ALT, increases in bilirubin, AST and/or ALT during the study have been evaluated in the context of haemolysis. Any liver function test elevation felt to be associated with haemolysis (and not caused by study drug) was not included in study stopping decisions.

Liver enzyme elevation is considered an adverse drug reaction (ADR) with danicopan. The mechanism for which danicopan causes elevation is not yet known.

**PNH Add-on Population**

As of the cutoff date 31 Mar 2022, 6 (6.3%) participants in the PNH Add-on Population reported at least 1 TEAE leading to study treatment/study discontinuation. Two of the 6 participants (both from Study ALXN2040-PNH-301; 1 receiving 150 mg tid danicopan and 1 receiving 200 mg tid danicopan) discontinued due to protocol-specified stopping criteria associated with abnormal liver enzyme laboratory values.

**All PNH Population**

One participant in the PNH Monotherapy Population experienced TEAEs leading to study treatment/study discontinuation (ALT and AST increased and BTH). Overall, 6.6% of participants in the All PNH Population experienced TEAEs leading to study treatment/study discontinuation.

To sum up, most discontinuation cases were due to liver enzyme elevations, even if they did not met the prespecified stopping rule criteria described above.

*Laboratory findings*

During TP1 ALXN2040-PNH-301 study, most of the observed chemistry, haematology, coagulation, and urinalysis laboratory abnormalities (shifts from normal at Baseline to low or high) were not clinically meaningful. There was a slightly higher incidence of TEAEs associated with liver abnormalities in the add-on danicopan group (14.0%) compared with the placebo group (10.3%). In general, no clinically meaningful findings in clinical laboratory evaluations were observed. Grade 3 or Grade 4 abnormalities were low, although were considered clinically meaningful. The liver enzyme elevations should be monitored.

*Hepatotoxicity assessment*

**ALXN2040-PNH-301**

Based on laboratory data from all participants, the following postbaseline elevations in ALT were observed during TP1: A higher incidence of ALT elevations (> 3 × ULN) was reported in the danicopan group (14.0%) compared with placebo group (3.4%). Eight participants in the danicopan group had ALT > 3 × ULN as the highest post Baseline value. There was 1 participant in the danicopan group with ALT > 3 × ULN and total bilirubin > 2 × ULN. There was no TEAE reported. Treatment with danicopan was continued, and values decreased to reference ranges. These laboratory findings were not considered as meeting Hy's Law criteria. Additional safety analyses using ALT and total bilirubin data were performed to assess for drug induced serious hepatoxicity (DISH). The TP1 eDISH plot showed in 3 participants, 2 from the add-on danicopan group and 1 from the placebo group. These findings were not considered a Hy's Law case.

However, a remarkable number of patients are still at risk of DILI (Temple's Corollary Range).

**PNH Add-on Population**

Post baseline elevations in ALT were observed in the PNH Add-on Population: fifteen (15.6%) participants had 36 occurrences of ALT > 3 × ULN as the highest post baseline value and, four (4.2%) participants had ALT > 3 × ULN and total bilirubin > 2 × ULN, of which 3 (3.1%) had alkaline phosphatase < 2 × ULN. All are participants from Study ALXN2040-PNH-301. None of these cases met Hy's Law criteria upon further review.

**All PNH Population**

The following post-baseline elevations in ALT were observed in the All PNH Population: sixteen (15.1%) participants had 38 occurrences of ALT > 3 × ULN as the highest post baseline value. This population included 1 additional participant with ALT increased from the PNH Monotherapy Population. This participant experienced an SAE of ALT and AST increased concurrent with a serious event of breakthrough haemolysis. There were no participants with ALT > 3 × ULN and total bilirubin > 2 × ULN in the PNH Monotherapy Population.

Liver enzyme (LE) elevations are considered of AESI for PNH patient, since they experience LE elevations secondary to haemolysis as well. However, the present liver safety data of danicopan is rather limited in time.

*AEs of haemolysis and breakthrough haemolysis*

**Study ALXN2040-PNH-301**

In TP1 data cutoff 28 Jun 2022, 2 TEAEs of haemolysis (BTH) were reported in 2 participants. None of these events had LDH above 1.5 × ULN (upper limit of normal); none led to discontinuation of treatment. Both events resolved and were assessed as related to study intervention. As of the cutoff date 31 Mar 2023 there were no new reports of haemolysis in TP1.

**PNH Add-on Population**

As of the cutoff date 31 Mar 2023, there were 16 TEAEs of haemolysis (9 events of haemolysis and 7 of BTH) reported in 12 participants in the PNH Add-on Population based on the clinical judgement of the Investigator. None of the events led to discontinuation of study treatment. Four participants were on stable eculizumab (2 participants in Study ACH471-101 and 2 participants in Study ALXN2040-PNH-301) and 8 on ravulizumab (8 participants in Study ALXN2040-PNH-301) treatment.

**All PNH Population**

In the All PNH Population data cutoff 31 mar 2023, there were 26 events of haemolysis (11 events of haemolysis and 15 events of BTH) in 17 participants based on the clinical judgement of the Investigator. This includes 10 TEAEs of haemolysis (2 events of haemolysis and 8 of BTH) in 5 participants from the PNH Monotherapy Population. None of the events led to discontinuation of treatment.

The number and frequency of BTH events has not been studied as secondary or exploratory efficacy endpoint within the danicopan clinical studies. BTH and haemolysis have been presented as AEs by the Applicant in the Clinical safety Summary. Albeit BTH was not defined as AESI by the Applicant, its occurrence might have significance. Since PNH clone size increases due to the factor D inhibition, missed danicopan doses or treatment discontinuation might result in BTH, sometimes a catastrophic one. As of the cutoff date, there were a total of 10 participants with 14 events of haemolysis reported during the different treatment periods of the study (TP1, TP2, LTE): 8 haemolysis and 6 BTH. All events of haemolysis or BTH occurred during treatment with danicopan. Most of the events were non-serious, mild to moderate in severity, and considered unrelated to danicopan or background C5 inhibitor. All events resolved and none led to treatment discontinuation. The Applicant clarified that none of the patients discontinued danicopan therapy due to BTH, and no BTH events were observed after discontinuation of danicopan treatment. The danicopan taper was not implemented for prevention of BTH but as a risk mitigation measure for liver enzyme elevation. Nonetheless, all patients who are to discontinue are to do so through a taper. Since no BTH events were observed in the PNH-301 study after discontinuation of danicopan treatment (ravulizumab or eculizumab treatment was continued in these cases), and since danicopan will be used as an add-on treatment to ravulizumab or eculizumab, therefore occurring of BTH is considered unlikely.

*Safety in special populations*

The compared TEAEs profiles were generally similar by age, sex, race, geographic region, weigh and BMI. Most data were reported in the < 65 years of age group; however, similar incidences were observed in the 65 through 74 years and 75 through 84 years age groups although data on the use of danicopan in elderly patients are considered limited, especially in patients ≥ 75 years.

No dose adjustments are proposed in patients with mild to moderate renal impairment and in patients with mild to moderate hepatic impairment. In patients with severe renal impairment the recommended starting dose is 100 mg three times a day. This dose can be increased to 150 mg three times a day after a minimum of 4 weeks of treatment depending on clinical response. However, due to a higher

exposure with the 150 mg dose, these patients should be monitored for AEs (a warning has been included in section 4.4. of the SmPC). Danicopan is not recommended to be used in patients with severe hepatic impairment. A higher exposure was observed in subjects with severe renal impairment compared to subjects with normal renal function, which suggest that an alternative dosing regimen may be required in this subgroup of patients (see PK/PD section).

The use of danicopan in pregnant and lactating participants has not been studied. As a precautionary measure, the use of danicopan during pregnancy should be avoided. Besides, danicopan should not be used during breast-feeding.

*Other considerations*

Of note, ravulizumab (C5-inhibitors) has an important potential risk of malignancies and haematological abnormalities. Although the PD properties of danicopan are somewhat different, it is not anticipated that the risks may be different. It is deemed that those risks cannot be excluded. Regarding the safety concerns, malignancy/hematologic abnormalities has been included as an important potential risk in the list of safety concerns of RMP, which should be monitored and characterized through pharmacovigilance activities. Meningococcal infection and serious infections also considered as important potential risk in the RMP.

The safety profile of ravulizumab or eculizumab remained unchanged with danicopan add-on treatment. Overall, the incidence of any TEAE was similar between the C5 inhibitor background therapy subgroups, with 94.1% of eculizumab-treated and 94.0% of ravulizumab-treated participants experiencing at least 1 TEAE. There was a higher incidence of SAEs in eculizumab-treated participants (26.5%) compared to ravulizumab-treated participants (16.0%). The incidence of TEAEs leading to discontinuation was higher in ravulizumab-treated participants (8.0%) compared to eculizumab-treated participants (2.9%). The incidence of related TEAEs and TEAEs by severity was similar between these subgroups with most events considered unrelated and mild to moderate in severity.

The incidence of TEAEs was generally similar across the pooled treatment populations. The type of reported events considered related to the study intervention was similar across the different populations. The percentages of participants with Grade 1, 2, and 3 events were similar across populations. There was no increase in incidence of related TEAEs over time. The incidence of headache, pyrexia and upper respiratory tract infections appeared to have remained unchanged over time. There was no increased incidence of infections noted with longer treatment duration. No trend in severity of TEAEs was noted with longer treatment duration.

## 2.6.10. Conclusions on the clinical safety

The addition of danicopan to ravulizumab or eculizumab entails an increase in the overall incidence of AEs, although it does not seem to increase SAEs and AEs of grade ≥3. During TP1, the most frequent TEAEs reported in the add-on danicopan group were headache, nausea, diarrhoea and arthralgia. Of these, there were 21.1% of participants in the add-on danicopan group and 27.6% in the placebo group who experienced at least 1 TEAE considered related to the study intervention.

Liver enzymes elevations and hepatic toxicity are AESIs of concern with danicopan. BTH events are of significance. All events of haemolysis or BTH occurred during treatment with danicopan. Most of the events were non-serious, mild to moderate in severity, and considered unrelated to danicopan or background C5 inhibitor. All events resolved and none led to treatment discontinuation. None of the patients discontinued danicopan therapy due to BTH, and no BTH events were observed after discontinuation of danicopan treatment.

One of the limitations of this dataset is the lack of long term safety data beyond 24 weeks. Thus, following a recommendation from the CHMP, the applicant committed to submit results from the final CSR of study ALXN2040-PNH-301 to further characterise the safety profile of danicopan as add-on to ravulizumab or eculizumab in the long term (REC).

## *2.7. Risk Management Plan*

### 2.7.1. Safety concerns

**Table 98: Summary of safety concerns**

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | Meningococcal infection<br>Serious infections<br>Malignancies and haematologic abnormalities |
| Missing information | Use in pregnant and breastfeeding women<br>Use in patients with severe hepatic impairment-<br>Long-term safety |

### 2.7.2. Pharmacovigilance plan

**Table 99: Ongoing and planned additional pharmacovigilance activities**

| **Study**<br>**Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| Category 3 - Required additional pharmacovigilance activities | | | | |
| "An Observational Cohort Study to Assess Long-Term Safety of Danicopan Add-on Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria: Analysis of IPIG-Registry Data"<br>(ALX-PNH-502)<br>Planned | Primary objectives:<br>- Characterise the long-term safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with PNH<br>- Describe and compare the incidence of meningococcal infection in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy<br>- Describe and compare the incidence of serious infection in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and | - Meningococcal infection<br>- Serious infections<br>- Malignancies and haematologic abnormalities<br>- Use in pregnant and breastfeeding women<br>- Use in patients with severe hepatic impairment<br>- Long-term safety | Draft study protocol submission | 3 months post-approval |
| | | | First data extraction | Q4 2024 |
| | | | Interim study reports | Every 2 years throughout study conduct |
| | | | Final CSR submission | Q3 2031 |

| Study<br>Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| | 2) ULTOMIRIS or SOLIRIS monotherapy<br>- Describe and compare the incidence of malignancies and haematologic abnormalities in participants with PNH treated with 1) danicopan as add-on therapy to ravulizumab/eculizumab and 2) ULTOMIRIS or SOLIRIS monotherapy<br>- Characterise the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in participants with severe hepatic impairment<br>Secondary objectives:<br>- Characterise the safety profile of danicopan as add-on therapy to ravulizumab/eculizumab in pregnant participants, pregnant partners of participants, or participants who are breastfeeding<br>- Describe the demographic and clinical profile at treatment initiation in participants with PNH treated with danicopan as add-on therapy to ravulizumab/eculizumab<br>- Assess danicopan as add-on therapy to ravulizumab/eculizumab treatment discontinuation patterns among participants with PNH | | | |

| Study<br>Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| "A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Clinically Evident Extravascular Hemolysis (EVH)"<br>(ALXN2040-PNH-301)<br>Ongoing | Primary objective:<br>- To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor at 12 weeks<br>Safety objectives:<br>- To evaluate the safety and tolerability of 24 weeks of treatment with danicopan as add-on therapy to a C5 inhibitor<br>- To evaluate the safety and tolerability of danicopan as add-on therapy to a C5 inhibitor during the LTE period | - Long-term safety | Final CSR submission | Q1 2026 |
| "A Long-term Extension (LTE) Study to Characterize the Safety and Efficacy of Danicopan as an Add-on Therapy to a Complement Component 5 Inhibitor (C5i) in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Previously Treated with Danicopan in an Alexion-sponsored Clinical Study"<br>(ALXN2040-PNH-303)<br>Ongoing | Primary objective:<br>- To characterise the long-term safety of treatment with danicopan as an add-on therapy to a C5 inhibitor<br>Secondary objectives:<br>- To characterise long-term efficacy of danicopan as an add-on therapy to a C5 inhibitor<br>- To characterise the long-term effect of treatment with danicopan as an add on therapy to a C5 inhibitor on FACIT-Fatigue scores and on European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 Scale scores<br>- To further characterise the safety of danicopan as an add-on therapy to a C5 inhibitor | - Long-term safety | Final CSR submission | Q1 2029 |

C5, complement component 5; CSR, clinical study report; FACIT, Functional Assessment of Chronic Illness Therapy; IPIG, International PNH Interest Group; LTE, long-term extension; PNH, paroxysmal nocturnal haemoglobinuria; Q, quarter

## 2.7.3. Risk minimisation measures

**Table 100: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Meningococcal infection | Routine risk minimisation measure:<br>SmPC sections 4.3 and 4.4<br>PL sections 2 and 4<br>Signs and symptoms of meningococcal infection and steps to be taken should any of these occur are detailed in SmPC section 4.4 and the PL section 2.<br>The need for a vaccination (including the need for antibiotic prophylaxis until 2 weeks after vaccination) is stated in SmPC section 4.4. and PL section 2.<br>Subject to restricted medical prescription. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>Specific adverse reaction follow-up questionnaire<br><br>Additional pharmacovigilance activities:<br>ALX-PNH-502 (final CSR: Q3 2031) |
| Serious infections | Routine risk minimisation measure:<br>SmPC section 4.4<br>PL sections 2 and 4<br>Subject to restricted medical prescription. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br><br>Additional pharmacovigilance activities:<br>ALX-PNH-502 (final CSR: Q3 2031) |
| Malignancies and haematologic abnormalities | Routine risk minimisation measure:<br>Subject to restricted medical prescription | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br><br>Additional pharmacovigilance activities:<br>ALX-PNH-502 (final CSR: Q3 2031) |
| Use in pregnant and breastfeeding women | Routine risk minimisation measure:<br>SmPC sections 4.6 and 5.3<br>PL section 2<br>The recommendation for the use of effective contraception during treatment and until 3 days after discontinuation is included in SmPC section 4.6 and PL section 2.<br>Subject to restricted medical prescription. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>Specific adverse reaction follow-up questionnaire<br><br>Additional pharmacovigilance activities:<br>ALX-PNH-502 (final CSR: Q3 2031) |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Use in patients with severe hepatic impairment | Routine risk minimisation measure:<br>SmPC sections 4.2, 4.4, and 5.2<br>Subject to restricted medical prescription. | Additional pharmacovigilance activities:<br>ALX-PNH-502 (final CSR: Q3 2031) |
| Long-term safety | Routine risk minimisation measure:<br>Subject to restricted medical prescription | Additional pharmacovigilance activities:<br>ALX-PNH-502 (final CSR: Q3 2031)<br>ALXN2040-PNH-301 (final CSR: Q1 2026)<br>ALXN2040-PNH-303 (final CSR: Q1 2029) |

CSR, clinical study report; PL, Package Leaflet; PNH, paroxysmal nocturnal haemoglobinuria; SmPC, Summary of Product Characteristics.

### 2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.5 is acceptable.

## *2.8. Pharmacovigilance*

### 2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18.01.2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Taking into consideration the configuration of the blister sealed into the inner wallet card, the Group agreed with a full omission of particulars in that case. In addition, the use of the minimum particulars on the bottles was deemed acceptable due to the small dimensions of the bottle label.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages, but will appear in grey-shaded to show that they will not be included on the printed materials.

### 2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Voydeya (danicopan) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The approved indication is

- Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia (see section 5.1).

### 3.1.2. Available therapies and unmet medical need

PNH is characterized by destruction of RBCs (haemolytic anaemia), blood clots (thrombosis), impaired bone marrow function, and haemolysis. The typical clinical hallmark of PNH is complement-mediated intravascular haemolysis (IVH) of the RBCs.

The C5 inhibitors eculizumab and ravulizumab represent the standard treatment option for patients with PNH. Both are monoclonal antibodies that specifically target C5 terminal complement cascade and inhibit its cleavage during complement activation into C5a and C5b. Eculizumab and ravulizumab have increased survival and improved outcomes in PNH by controlling IVH. However, some patients with PNH who achieve durable IVH control and associated disease control with ravulizumab or eculizumab may experience clinically significant EVH. EVH occurs in approximately 20% of C5i treated patients, with approximately 10% of these patients requiring RBC transfusions.

The currently approved treatment for patients with PNH experiencing EVH is the C3 inhibitor pegcetacoplan (Aspaveli). Pegcetacoplan is approved in the EU as monotherapy for the treatment of adult patients with PNH who have haemolytic anaemia.

### 3.1.3. Main clinical studies

The pivotal study is **study ALXN2040-PNH-301**, a randomized, double-blind, placebo-controlled, multiple-dose, Phase 3 study in participants with PNH who have clinically significant EVH (Hgb $\leq$ 9.5 g/dL with absolute reticulocyte count $\geq$ 120 $\times$ $10^9$/L) while on treatment with background eculizumab or ravulizumab.

The study consisted of one randomised treatment period up to Week 12 (TP1) in which patients were randomised (2:1) to receive either danicopan or placebo, in addition to their background therapy with eculizumab or ravulizumab and an open-label treatment period up to Week 24 (TP2) in which patients receiving placebo in TP1 switched to receive danicopan and patients receiving danicopan continue to receive danicopan. Patients who completed TP2, may enter the Long-Term Extension Period (LTE), up to a maximum of 2 years.

The primary endpoint of the study was the change in haemoglobin (Hgb) from baseline to week 12. Key secondary endpoints were the proportion of patients with Hgb increase ≥2 g/dL (20 g/L), proportion of patients with transfusion avoidance, change from baseline in FACIT-Fatigue scores and change from baseline in absolute reticulocyte count, all assessed at week 12.

As of the data cut-off date for the first IA (28 Jun 2022) 73 patients had been randomised to danicopan (n=49) or placebo (n=24), of which 63 patients are included in the interim efficacy analysis set. Results of a third IA (DCO: 31 Mar 2023) were submitted during the procedure. At the time of IA3 86 patients had been enrolled in the study. Efficacy data presented below are based on IA3 of a modified randomised population (n=83).

## *3.2. Favourable effects*

The primary evidence for efficacy analysis is based on a pre-specified analysis performed when the first 63 randomised participants reached the end (either completed or discontinued) of the 12-week treatment period 1. Danicopan as an add-on to ravulizumab or eculizumab was superior to placebo as an add-on to ravulizumab or eculizumab for the primary endpoint and resulted in a statistically significant increase in Hgb from baseline to week 12. The LS mean change in Hgb from baseline was 2.94 g/dL [1.82 mmol/L] in the danicopan group compared with 0.50 g/dL [0.31 mmol/L] in the placebo group. The treatment group difference was 2.44 g/dL [1.51 mmol/L] (95% CI: 1.69 [1.05], 3.20 [1.99]); p < 0.0001).

Danicopan also achieved statistically significant improvement compared to placebo for all 4 secondary endpoints: proportion of patients with Hgb increase of ≥ 2 g/dL [1.2 mmol/L] in the absence of transfusion (59.5% vs. 0%, treatment difference: 46.9 [95% CI: 29.2, 64.7]; p < 0.0001), proportion of patients with transfusion avoidance (83.3% vs. 38.1%, treatment difference: 41.7 [95% CI: 22.7, 60.8]; p = 0.0004), change in FACIT-Fatigue score (7.97 vs. 1.85, treatment difference: 6.12 [95% CI: 2.33, 9.91]; p = 0.0021) and change in absolute reticulocyte count (-83.8 vs. 3.5, treatment difference: -87.2 [95% CI: -117.7, -56.7]; p < 0.0001).

## *3.3. Uncertainties and limitations about favourable effects*

One of the limitations of the study is the small sample size, although it was considered acceptable taking into account the rarity of the disease. Moreover, the effect of danicopan seems to be maintained in the long term, although data beyond 24 weeks are still considered limited. The Applicant committed to providing the final CSR by Q1 2026 (REC) although interpretation of long-term efficacy data is hampered by the absence of a control arm.

## 3.4. Unfavourable effects

The safety evaluation supporting the use of danicopan as an add-on to ravulizumab or eculizumab for the treatment of patients with PNH is based a pivotal study ALXN2040-PNH-301 and a pooled safety analysis. In total, 57 patients were treated with danicopan in this phase 3 clinical trial during the randomised treatment period (TP1).

The most frequently reported AEs by System Organ Class (SOCs) in TP1 Study ALXN2040 PNH 301 were gastrointestinal disorders (29.8%), musculoskeletal and connective tissue disorders (17.5%), investigations (14.0%), nervous system disorders (12.3%), and general disorders and administration site conditions (10.5%) and vascular disorders (8.8%).

In TP1, the incidence of TEAEs was similar between the 2 treatment groups (75.4% add-on danicopan group vs. 62.1% add-on placebo group). There was a slightly higher incidence of TEAEs related to liver abnormalities in the add-on danicopan group (14.0%) compared to the placebo group (10.3%). In TP2, the incidence of TEAEs was 70.7%. The most frequent TEAEs in the add-on danicopan group were headache (10.5%), nausea (8.8%), and diarrhea and arthralgia (7.0% each). The TEAEs for which the incidence was ≥ 5% in the add-on danicopan group, and higher than the placebo group, were vomiting, pyrexia, urinary tract infection, ALT increased, arthralgia, pain in extremity, headache, and hypertension. There were 21.1% of participants in the add-on danicopan group and 27.6% in the placebo group who experienced at least 1 TEAE considered related to the study intervention. The most frequently reported treatment-related TEAEs in the add-on danicopan group (> 3%) were nausea (7.0%), pyrexia, ALT increased, AST increased, and headache (3.5% each).

Grade 3 TEAEs were reported in 17.5% of participants in the add-on danicopan group versus 13.8% of participants in the placebo group. No deaths and no cases of meningococcal infections were reported.

Regarding AESIs, 8 (14.0%) participants experienced 13 TEAEs in the add-on danicopan group and 3 (10.3%) participants experienced 5 TEAEs in the placebo group. There were 3 (5.3%) participants in the danicopan arm and 2 (6.9%) in the placebo group who experienced at least 1 SAE. A higher incidence of ALT elevations was reported in the danicopan group (14.0%) compared with placebo group (3.4%).

## 3.5. Uncertainties and limitations about unfavourable effects

The safety database is deemed limited in terms of number of PNH patients exposed due to the rarity of the disease, the limited data available in the long term and the lack of comparative long-term safety data. In order to further characterise the safety profile of danicopan as add-on to ravulizumab or eculizumab the final CSR of study ALXN2040-PNH-301 should be submitted post-approval.

According to danicopan mode of action, the risk of serious infections (other than meningococcal infections), may be increased in patients treated with danicopan. Further, it is important to note that danicopan is given as add-on to ravulizumab or eculizumab and therefore the risk of serious infections may be even higher. Thus, "serious infections" is considered an important potential risk for danicopan.

Moreover, "malignancies and haematological abnormalities" are important potential risks of C5-inhibitors. Since danicopan is given an add-on to ravulizumab or eculizumab for the treatment of patients with PNH, then, malignancies and haematologic abnormalities have also been included as an important potential risk.

Data on the use of danicopan in elderly patients are considered limited, especially in patients ≥ 75 years.

## 3.6. Effects Table

**Table 101: Effects Table for Voydeya (danicopan) in the treatment of PNH (data cut-off: 31 Mar 2023).**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| ***Primary endpoint*** | | | | | | |
| Change in Hbg at week 12 | Change in Hbg relative to baseline after 12 weeks of treatment with danicopan compared with placebo | Mean (g/dL) | 2.81 | 0.41 | Treatment difference (LS mean): 2.40 (95% CI:1.68, 3.13); p<0.0001 | CSR |
| ***Key secondary endpoints*** | | | | | | |
| Patients with Hbg≥2 g/dL at week 12 | Proportion of patients with Hgb increase ≥2 g/dL at week 12 in the absence of transfusions | % | 54.4 | 0 | Treatment difference: 46.9 (95% CI: 31.45, 62.36); p < 0.0001. | |
| Tranfusion avoidance at week 12 | Proportion of patients with transfusion avoidance at week 12 | % | 78.9 | 30.8 | Treatment difference: 46.4 (95% CI: 29.30, 63.53); p =0.0001 | |
| Change in FACIT-Fatigue at week 12 | Change from baseline in FACIT-Fatigue scores at week 12 | | 8.00 | 2.29 | Treatment difference: 5.71 (95% CI: 2.56, 8.86); p=0.0006 | |
| Change in ARC at week 12 | Change from baseline in absolute reticulocyte counts at week 12 | $10^9$/L | -93.1 | -3.4 | Treatment difference (LS mean): -89.6 (95% CI:-118.5, -60.8); P< 0.0001 | |
| **Unfavourable Effects - Study ALXN2040-PNH-301-TP1** | | | | | | |
| TEAEs | Treatment-emergent adverse events | % | 75.4 | 62.1 | | (1) |
| Related-TEAE | Treatment-emergent adverse events related to study | % | 21.1 | 27.6 | | (1) |
| Grade 3 TEAE | Treatment-emergent adverse events grade 3 | % | 17.5 | 13.8 | | (1) |
| Grade 4 TEAE | Treatment-emergent adverse events grade 4 | % | 1.8 | 0 | | (1) |
| SAEs | Serious adverse events | % | 5.3 | 6.9 | | (1) |

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| EA leading to withdrawal of study intervention | Treatment-emergent adverse events leading to withdrawal of study intervention | % | 5.3 | 3.4 | | (1) |
| Headache | Common adverse event | % | 10.5 | 10.3 | | (1) |
| Nausea | Common adverse event | % | 8.8 | 10.3 | | (1) |
| Diarrhoea | Common adverse event | % | 7.0 | 10.3 | | (1) |
| Arthralgia | Common adverse event | % | 7.0 | 6.9 | | (1) |
| Liver enzyme elevations | Adverse event of special interest | % | 14.0 | 10.3 | | (1) |
| Meningococcal infections | Adverse event of special interest | % | 0 | 0 | | (1) |

Abbreviations: CSR=clinical study report; Hgb=haemoglobin

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

In the study ALXN2040-PNH-301 danicopan as add-on to ravulizumab or eculizumab achieved a statistically significant improvement in the mean change in Hgb at week 12 relative to baseline, compared with placebo. Results of the key secondary endpoints and other secondary endpoint supported the primary analysis. Of note, an improvement was observed regarding transfusions avoidance in patients receiving danicopan. However, data in the long term are still limited. The final CSR will be provided once available.

From a safety point of view the addition of danicopan to ravulizumab or eculizumab entails an increase in the overall incidence of AEs, although it does not seem to increase SAEs and AEs of grade ≥3. The most frequently reported AEs were headache diarrhoea, nausea, and arthralgia. Liver enzymes elevations is considered an AESI of danicopan. However, as for efficacy data, at the time of analysis, long term safety data were still limited.

### 3.7.2. Balance of benefits and risks

The efficacy results show important benefits of danicopan as add-on to eculizumab or ravulizumab in patients with PNH after 12 weeks of treatment. The safety profile was overall manageable. As a result, the benefit-risk balance is considered positive.

### 3.7.3. Additional considerations on the benefit-risk balance

Patient representatives provided their feedback and highlighted the relevance of extreme fatigue that remains despite treatment and normalized life expectancy. In addition to fatigue, they are concerned about the impact of the disease on their quality of life, many of them being forced to discontinue their jobs, which leads to depression and social isolation.

In addition, they compared the different treatment alternatives available. For eculizumab they note that they have to go to the hospital for the infusion of the drug every two weeks, which causes them anxiety and lack of freedom. For ravulizumab, the efficacy perception is the same as for eculizumab, but they recognize as an advantage that the infusions in the hospital centre are every 8 weeks, which reduces their anxiety levels.

As for the expectations of the new treatments, they recognize that the oral route would be an advantage over the infusion, but what they would mainly value would be an improvement in the extreme fatigue. They also expect disease registries that would evaluate quality of life/fatigue.

The contribution of patient representative is highly appreciated.

## *3.8. Conclusions*

The overall benefit/risk balance of Voydeya is positive subject to the conditions stated in section 'Recommendations'.

# 4. Recommendations

***Similarity with authorised orphan medicinal products***

The CHMP by consensus is of the opinion that Voydeya is not similar to Aspaveli within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Voydeya is favourable in the following indication(s):

- Voydeya is indicated as an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who have residual haemolytic anaemia (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States***

Not applicable.

***New active substance status***

Based on the CHMP review of the available data, the CHMP considers that danicopan is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.