swissmedic

Date: 9 July 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Voydeya

International non-proprietary name: danicopan
Pharmaceutical form: film-coated tablets
Dosage strength(s): 50 mg, 100 mg
Route(s) of administration: oral
Marketing authorisation holder: Alexion Pharma GmbH
Marketing authorisation no.: 69301
Decision and decision date: approved on 30 April 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BID	Bis in die: twice a day
CAP	Complement alternative pathway
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
EVH	Extravascular haemolysis
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
Hgb	Haemoglobin
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
LTE	Long-term extension
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal haemoglobinuria
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TID	Ter in die: 3 times a day

TP	Treatment period
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for danicopan in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 1 June 2023.

2.2 Indication and dosage

2.2.1 Requested 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).

2.2.2 Approved indication

Voydeya is used as an add-on to ravulizumab or eculizumab for the treatment of clinically relevant extravascular haemolysis (EVH, as defined in current clinical guidelines) after at least 6 months of monotherapy with a C5 inhibitor in adult patients with paroxysmal nocturnal haemoglobinuria (PNH; see "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:

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.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	17 May 2023
Formal objection	21 May 2023
List of Questions (LoQ)	25 July 2023
Response to LoQ	2 October 2023
Preliminary decision	21 November 2023
Response to preliminary decision	9 February 2024
Labelling corrections	29 February 2024
Response to labelling corrections	14 March 2024
2nd labelling corrections	3 April 2024
Response to 2nd labelling corrections	17 April 2024
Final decision	30 April 2024
Decision	approval

3 Medical context

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematological disease with an incidence of 1-1.5/ 1 million (international data, no exact data for Switzerland available). Clinical presentation varies considerably. Symptoms comprise haemolytic anaemia, thrombosis, renal impairment, and fatigue, amongst others[1].

PNH is characterised by acquired (somatic) mutations of the PIG-A gene in pluripotent haematologic stem cells and other, not fully understood, mechanisms. Ultimately, this results in glucose phosphate isomerase (GPI)-deficient peripheral blood cells. The GPI anchor is essential for linking certain membrane proteins in eukaryotic cells. In PNH pathogenesis, the resulting deficiency of complement-regulating proteins (in particular CD55 and CD59) on erythrocytes is of particular relevance. This deficiency leads to complement-mediated lysis of erythrocytes. Lysis may be intravascular and extravascular.

PNH is a serious and potentially life-threatening disease. Historical retrospective data from a UK cohort demonstrate a reduced life expectancy of PNH patients[2].

The central role of the complement system in PNH has led to the successful use of complement inhibitors in the treatment of PNH.C5 inhibition, which mainly inhibits intravascular lysis, is currently the standard first-line treatment for symptomatic PNH patients. Treatment is combined with supportive therapy, including anticoagulation.

The only curative treatment option for this disease remains allogeneic haematopoietic stem cell transplantation. However, nowadays this is only recommended if PNH is associated with aplastic bone marrow deficiency (aplastic anaemia).

[1] Schubert J. Paroxysmale nächtliche Hämoglobinurie (PNH), Onkopedia Leitlinie März 2022
[2] Hillmen P. et al., N Engl J Med 1995; 333:1253-1258

4 Quality aspects

4.1 Drug substance

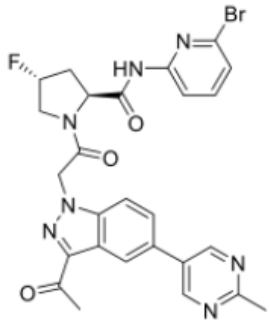
INN: Danicopan

Chemical name: (2S,4R)-1-{[3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl]acetyl}-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide

Molecular formula: $C_{26}H_{23}BrFN_7O_3$

Molecular mass: 580.42 atomic mass units (amu)

Molecular structure:



Physicochemical properties: Danicopan is a white/off-white to pale yellow powder. Danicopan has 2 chiral centres and is manufactured as a single stereoisomer. The compound is assigned a low solubility according to the Biopharmaceutical Classification System (BCS).

Synthesis: The drug substance is manufactured by multiple step chemical synthesis. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification: In order to ensure consistent quality of danicopan, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines.

Stability: The bulk drug substance is packaged in low-density polyethylene (LDPE) bags. A stability study, carried out according to the current guideline recommendations, was carried out. Based on the results of this study, a satisfactory retest period was established.

4.2 Drug product

Description and composition: Danicopan film-coated tablets are manufactured in strengths of 50 mg and 100 mg. The 50 mg tablets are presented as white to off-white round tablets with “DCN” above “50” debossed on one side and plain on the other side. The 100 mg tablets are presented as white to off-white round tablets with “DCN” above “100” debossed on one side- and plain on the other side.

Pharmaceutical development: Danicopan drug product was developed as an immediate-release oral tablet containing the following excipients: hypromellose acetate succinate, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

Manufacture: Danicopan film-coated tablets are manufactured as spray-dried dispersion drug product. Adequate process parameters and in-process controls are defined in order to ensure consistent quality of the tablets.

Specification: For the control of the finished product, adequate tests and criteria for release and at shelf-life are established. The test methods applied are adequately validated according to the recommendations of the current scientific guidelines.

Container closure system: The primary container closure system used for commercial distribution of danicopan tablets is a high-density polyethylene (HDPE) bottle packaging with a polypropylene (PP) cap and contains a desiccant. In addition, a blister pack is also used for marketing.

Stability: Appropriate stability data are presented for both the 50 and 100 mg tablets. Based on these data, a shelf-life was established. The storage recommendation is “Do not store above 30°C”.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Danicopan bound to the active site of human Factor D (FD) with a K_D of 0.540 nM and inhibited the catalytic activity of human FD protein with an IC_{50} value of 0.018 µM and a K_i of 5.7 nM.

Inhibition of the complement alternative pathway (CAP) by danicopan was determined using 2 different functional endpoints, *i.e.*, haemolysis of heterologous erythrocytes as well as assembly and deposition of terminal complement complex (TCC) following CAP activation (IC_{50} values < 1 µM). The compound also inhibited C3 fragment deposition (IC_{50} < 0.1 µM). The applicant compared danicopan and eculizumab, and showed that both compounds fully inhibited the formation of TCC. Danicopan was selective for the CAP; there was no inhibition of the complement classical pathway (CCP) or complement lectin pathway (CLP) activity in corresponding functional assays.

Analyses of serum samples from repeat-dose toxicity studies (in dogs) and an embryo-fetal development (EFD) study (in rabbits) confirmed that the repeated dosing caused a rapid and complete inhibition of CAP activity in both species, identifying them as pharmacologically relevant. The metabolites M173 and M426 neither contributed to the pharmacological action nor did they exert any cytotoxicity.

The applicant provided nonclinical data for the combination of danicopan with eculizumab, and the combination with ravulizumab was investigated in clinical studies.

Danicopan did not cause cellular toxicity and did not interact with a selection of other serum proteases, receptors, or transporters at a concentration of 10 µM, except for the human adenosine receptors A_1 and A_3, and the human MT_1 melatonin receptor. Follow-up investigations did not identify any cause for concern.

The compound had only very limited impact on bactericidal activity of human serum compared to other C5 inhibitors. The *in vitro* and *in vivo* safety pharmacology investigations did not raise any concerns for the cardiovascular, central nervous, or respiratory systems.

5.2 Pharmacokinetics

Danicopan concentrations were determined using LC-MS/MS in plasma from mice, rats, rabbits, and dogs (to support the GLP toxicity studies) as well as in rabbit milk (non GLP). The applicant submitted a plethora of pharmacokinetic studies, which showed rapid absorption, extensive distribution, and moderate clearance of the compound. Plasma half-life was between 1 to 2 hours in rats and dogs.

Quantitative whole-body autoradiography in pigmented male rats indicated that the tissues with the highest exposure were *i.a.* the uvea, stomach, pigmented skin, liver, intestinal tissues, adrenal gland, urinary bladder, kidney cortex and medulla, mammary gland region, and thyroid. The tissues with the lowest concentrations were the brain, spinal cord, bone, testis, and lens of the eye. Patterns of distribution in nonpigmented rats were similar to those in pigmented rats, but tissue concentrations were generally lower at 1 hour post-dose. The observed differences in concentration between pigmented and non-pigmented tissues indicated that there was a specific but reversible association of danicopan-derived radioactivity with melanin. The applicant confirmed this in ocular distribution studies in rabbits as well as a melanin binding study *in vitro*.

Plasma protein binding in mice, rats, rabbits, dogs, and monkeys did not indicate any concentration dependency. Approximative free fractions were 7% in mouse, 12% in rat, 10% in rabbit, 18% in dog, 5% in monkey, and 9% in human plasma. Danicopan mainly bound to human serum albumin and not to human α1 acid glycoprotein; concentration in plasma was greater than estimated in blood cells.

In a lactational/placental transfer study, oral administration of 50 or 250 mg/kg/day danicopan to pregnant rabbits led to an exposure of all maternal and fetal animals on gestation day (GD) 19. The compound was detected in milk from treated rabbits; mean milk-to-maternal plasma ratios were 3.5 to 5.5 on lactation days (LD) 9 and 10. Danicopan was also present in plasma from pups at the 250 mg/kg/day dose on LD 10.

The metabolic stability of danicopan was investigated *in vitro* using liver microsomes and hepatocytes from mice, rats, rabbits, beagle dogs, cynomolgus monkeys, and humans. Metabolites were identified *in vitro* and then confirmed *in vivo*. Based on the analysis of plasma samples from human subjects, M426 and M173 are considered relevant metabolites for safety assessment. Studies in rats and dogs showed adequate coverage of these metabolites.

In rats and dogs, faecal excretion was the principal excretion route of danicopan-derived radioactivity.

5.3 Toxicology

Danicopan was administered orally, in line with the intended clinical route of administration. The duration of the repeat-dose toxicity studies was up to 26 weeks (in rats) or 39 weeks (in dogs), which is appropriate for the intended chronic treatment. The applicant sufficiently characterised the pharmacodynamic and pharmacokinetic profile of rats, dogs, and rabbits, and identified dogs and rabbits as pharmacologically relevant.

In rats, no danicopan-related mortality was observed up to 1000 mg/kg/day. However, in the 39-week study in dogs, 4 animals at 150 mg/kg/day were euthanised prematurely due to poor and/or deteriorating condition. These animals had adverse findings in the liver (suggestive of cholestasis), adrenal gland, and/or thymus.

Rats primarily showed consequences of an adaptive response to increased metabolic enzyme expression at doses down to 200 mg/kg/day. This included increased liver and thyroid organ weights correlating with centrilobular or diffuse hepatocellular hypertrophy or follicular cell hypertrophy as well as isolated cases of follicular cell adenoma. Clinical chemistry investigations showed an increase in cholesterol and thyroid stimulating hormone (TSH), and a decrease in thyroxine. In dogs, individual females in the high-dose group (*i.e.*, 150 mg/kg/day) had increased liver enzymes suggestive of hepatobiliary damage, partially correlating with bile duct hypertrophy/hyperplasia that occurred at doses ≥100 mg/kg/day, as well as pigment deposits in the Kupffer cells. Furthermore, high-dose animals had a decreased red blood cell count, haemoglobin, and haematocrit, as well as decreases in lymphocytes suggestive of dehydration and stress. There were no microscopic correlates and all findings were reversible. Danicopan did not adversely affect growth plates in the femur and tibia. The safety margins were > 5 in dogs and > 20 in rats in the pivotal chronic toxicity studies.

Danicopan was not genotoxic in a series of *in vitro* and *in vivo* assays.

The carcinogenic potential was addressed in a 2-year study in rats and a 26-week study in transgenic rasH2 mice. In the rat study, danicopan was administered at doses up to 500 mg/kg/day. The observed tumour incidences were within the range reported in the in-house historical control database or were adequately addressed, raising no concerns. Danicopan was not carcinogenic in rasH2 mice at doses up to 1500 mg/kg/day. The safety margins regarding carcinogenicity were >15 (rats) and >48 (mice).

In the fertility and early developmental (FEED) study in rabbits, lower mean male fertility and copulation indices were noted at the high-dose level (500 mg/kg/day). No effects on spermatogenesis endpoints were observed in this study or in the 39-week study in dogs. Females also showed significantly lower fertility and conception indices at the 500 mg/kg/day dose. Intrauterine survival of the embryos was unaffected by danicopan treatment at any dose level. In the pivotal EFD studies in rabbits and rats with doses up to 1000 mg/kg/day from GD 7 to GD 20 (rabbits) or GD 17 (rats), no danicopan-related fetal malformations or variations were observed. In both species, fetal weight was decreased at 1000 mg/kg/day. There were no test article-related external, visceral, or skeletal developmental variations or malformations. In the pre- and postnatal development (PPND) study, rabbits were treated with doses up to 250 mg/kg/day from GD 7 through LD 41. Overall, the treatment was well tolerated by the dams, and gestation length or reproductive performance was not impacted. Achievement of developmental landmarks was comparable in theF1 generation and the control group, and the reproductive performance of the F1 animals was not affected by the earlier exposure to

danicopan. The safety margins were 8 for the FEED study in rabbits, and 18 and 28 respectively for the EFD studies in rabbits and rats. No toxicokinetic data were available for the PPND study.

In a 6-week dose range-finding study in juvenile dogs, 1 male at 500 mg/kg/day was euthanised. As in adult animals, the liver was identified as the target organ.

Danicopan was not phototoxic in an *in vitro* and *in vivo* assay.
Regarding impurities, 4 impurities are specified above the qualification threshold and were adequately qualified.

Voydeya does not pose a risk for the environment.

The nonclinical safety specifications in the RMP adequately reflect the nonclinical findings.

5.4 Nonclinical conclusions

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Voydeya with the new active substance danicopan in the proposed indication. The pharmacological properties as well as the pharmacokinetic and toxicity profiles of danicopan were adequately characterised. All nonclinical data that are relevant for safety are included in the information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Biopharmaceutical development
The planned commercial formulation of danicopan is an immediate-release tablet formulation that was used in pivotal study ALXN2040-PNH-301. Therefore, there is no need for a bioequivalence study bridging the intended commercial product to the clinical product with which the Phase 3 study was performed.

Absorption
Following oral administration, danicopan is rapidly absorbed, with median T_{max} values ranging from 1.5 – 2.5 h across single and multiple dose administration (single doses: 200 to 1200 mg; multiple doses: 200 – 800 mg bid and 75 mg tid). An absolute bioavailability study was not conducted. Data from a mass balance study indicate a minimum absolute danicopan bioavailability of approximately 25% based on radioactivity recovered in urine.

Following administration of the proposed danicopan dose of 150 mg or 200 mg tid, steady state is generally reached on day 2 of dosing, with moderate accumulation (< 2-fold increase) given the tid dosing, the danicopan elimination half-life, and an absence of time-dependent danicopan PK (i.e. no danicopan-mediated auto-induction or inhibition).

Dose proportionality
Increases in both C_{max} and $AUC_{0\text{-}inf}$ appeared to be slightly less than dose proportional over the tested single dose range of 200 to 1200 mg and proportional over the tested multiple dose range of 200 to 800 mg bid. In the narrower clinically relevant dose range of 100 to 200 mg tid, however, dose proportionality for both C_{max} and AUC_{tau} can be assumed.

Distribution
Plasma protein binding of danicopan is high, with the free fraction values ranging from 5.5 to 8.7% (i.e. protein binding of 91.5 to 94.3%). The volume of distribution at steady state (V_{ss}/F) was calculated to be 165 L/F based on popPK analyses. The mean ratio of $AUC_{0\text{-}inf}$ based on plasma and whole blood radioactivity was 0.545, suggesting limited partitioning of [^{14}C] danicopan-derived radioactivity into blood cells.

Metabolism
Danicopan is extensively metabolised after oral dosing, predominantly via oxidation, reduction, and hydrolysis pathways (96% of the metabolism), resulting in a high number of pharmacologically inactive metabolites. Metabolism by CYP-mediated pathways is minimal (4 % of the metabolism), which substantially diminishes the drug-drug interaction potential of danicopan as a victim.

Elimination/excretion:
Faecal excretion is the predominant excretion route (69% of the radioactive dose), while urinary excretion accounts for 25% of the radioactive dose. Unchanged danicopan contributed approximately 23% of total radioactivity exposure in plasma, 1% in urine, and 4.5% in faeces. Metabolite M8, an amide hydrolysis product, was the major circulating plasma metabolite, contributing approximately 53% of total radioactivity exposure. Metabolite M8 was the major metabolite in urine, with 55% of the urinary radioactivity, and in faeces, with 55% of faecal radioactivity. The elimination half-life for danicopan was approximately 8 h in a typical 75 kg, white, male patient with normal organ function according to the popPK analysis.

Special populations
Two dedicated studies were submitted in patients with impaired hepatic and renal function in support of the proposed dosing recommendations (no dose adjustments in renally impaired patients and in patients with mild or moderate hepatic impairment).

In addition, dedicated studies indicated similar PK in healthy Japanese volunteers vs. healthy Caucasian volunteers, and in elderly volunteers vs. normal volunteers.

The impact of additional covariates was further investigated in popPK analyses based on danicopan concentration data from 14 studies (11 Phase 1, 2 Phase 2, and 1 Phase 3). A 2-compartmental model with linear elimination described the danicopan PK adequately. The analysis included 7195 danicopan PK samples from 407 subjects.

No impact on danicopan PK was found based on age, race and country (Japan vs non-Japan), region (East Asia vs non-East Asia), population (healthy subject vs PNH patients), hepatic function (moderate hepatic impairment), albumin, haemoglobin, factor D, and concomitant administration of C5 inhibitors. Modest decreases in exposure with increased weight (less than 20% in C_{max}, C_{min}, and AUC) and modest increases in AUC (29%) were observed in female vs. male subjects. These changes were not considered clinically meaningful and did not require danicopan dose adjustment.

Interactions
Overall, the available *in vitro* and *in vivo* data indicate a low interaction potential of danicopan and its metabolites. For further details see the information for healthcare professionals in the appendix of this report.

Secondary pharmacology (safety)
A dedicated QT/QTc study with single oral doses of 400, 800, and 1200 mg danicopan (up to 6-fold the therapeutic dose) indicated the absence of a QT/QTc interval prolongation potential induced by danicopan.

6.2 Dose finding and dose recommendation

The Phase 2 studies ACH471-100 and ACH471-101 contain elements of dose finding (dose escalation). Study ACH471-100 included complement inhibitor naïve patients, whereas study ACH471-101 included patients with insufficient response to C5 inhibitors, similar to the pivotal Phase 3 study ALXN2040-PNH-301.

Twelve patients were enrolled in study ACH471-101 (proof-of-concept study) at different starting doses of 100 mg 3 times daily (tid) or 150 mg tid as an add-on to eculizumab. Eleven patients completed the 24-week treatment period and were included in the primary efficacy analysis. Dose escalation up to 200 mg tid was allowed.

6.3 Efficacy

The applicant submitted the pivotal Phase 3 study ALXN2040-PNH-301 of danicopan as an add-on therapy to a C5 inhibitor (eculizumab or ravulizumab) in patients with paroxysmal nocturnal haemoglobinuria (PNH) who have clinically evident EVH in support of the application for the proposed indication.

Study ALXN2040-PNH-301 is an ongoing multiple-region, randomised, double-blind, placebo-controlled, multiple dose, Phase 3 study. This study includes patients with PNH, who have clinically significant extravascular haemolysis (EVH, defined as Hgb ≤ 9.5g/dL and reticulocyte counts >120x10^9/L) despite treatment with stable doses of ravulizumab or eculizumab for at least 6 months. The study consists of 2× 12-week-treatment periods (TP1 and TP2), and a 2-year long-term extension (LTE) period.

Patients were randomised to receive danicopan 3 times daily (tid) or placebo tid in a 2:1 ratio for 12 weeks, in addition to their background ravulizumab or eculizumab therapy (continued according to their usual dose and schedule throughout the study). At the end of Week 12 (end of TP1), participants randomised to receive placebo were switched to receive danicopan up to Week 24, while participants receiving danicopan continued to receive danicopan for an additional 12 weeks (TP2). After completion of TP2 (Week 24), participants could enter the LTE at the same danicopan dose received at Week 24. Background C5 inhibition was continued in all study periods.

The primary endpoint of the study was the change in haemoglobin (Hgb) levels relative to baseline after 12 weeks (TP1). Key secondary endpoints were the proportion of patients with Hgb increases ≥ 2g/dl, the proportion of patients with transfusion avoidance (TA), changes in FACIT fatigue score relative to baseline, and changes in reticulocyte counts relative to baseline, all within 12 weeks (TP1).

The first patient was randomised in January 2021. Efficacy results were presented based on the clinical data cut-off (DCO) of 20 September 2022 and updated efficacy results with a DCO of 31 March 2023.

In total, 86 patients were randomised 2:1. Fifty-seven patients were randomised to receive add-on danicopan from Week 1, and 29 patients were randomised to receive add-on placebo in TP1. As the switch to the verum was planned from TP2 onwards, a total of 80 patients were exposed to danicopan until the DCO of 20 September 2022.

Overall, baseline and disease characteristics were balanced between the treatment arms. For details, please refer to the attached information for healthcare professionals.

The add-on treatment with danicopan resulted in a statistically significant and clinically meaningful increase in Hgb from baseline to Week 12 compared with placebo. Using a mixed-effect model for repeated measures (MMRM), the least squares (LS) mean (standard error [SE]) increase in Hgb was 2.9 (0.2) g/dL in the danicopan group compared with 0.5 (0.3) g/dL in the placebo group. The treatment difference was maintained through to Week 12.

Twenty-five patients (59.5%) in the danicopan group had Hgb increases of ≥ 2.0 g/dL at Week 12 vs. no patients (0%) in the placebo group. Thirty-five patients (83.3%) achieved TA in the danicopan group compared with 8 patients (38.1%) in the placebo group. The LS mean (SE) change from baseline in FACIT-fatigue scores at Week 12 was 7.97 (1.128) in the danicopan group and 1.85 (1.581) in the placebo group; meaningful treatment differences in fatigue scores were seen from Week 8 onwards. The LS mean change from baseline in absolute reticulocyte count was - 83.8 × 10^9/L at Week 12 in the danicopan group and 3.5 × 10^9/L in the placebo group. The treatment group difference was -87.2 × 10^9/L.

After the initial 12-week treatment period TP1, the patients in the placebo arm were switched to danicopan treatment. For TP2, this resulted in a DAN/DAN group (danicopan in TP1 and TP2) and a PBO/DAN group (placebo in TP1 and danicopan in TP2). Efficacy analyses in Week 24 (at the end of TP2) suggest that the treatment effect in the DAN/DAN group was maintained in a substantial proportion of patients (but not increased). In the PBO/DAN group treatment effects comparable to that observed in the TP1 danicopan group were achieved.

Updated efficacy data were comparable to results at the DCO of 20 September 2022.

6.4 Safety

In treatment period 1 (TP1, first 12 weeks of treatment, blinded, randomised), 73.7% of patients in the danicopan group experienced any grade treatment-emergent adverse events (TEAE) vs 62.1% in the placebo group. In the danicopan group, 5.3% of patients had serious adverse events (SAEs) in TP1 vs 6.9% in the placebo group.

In the danicopan group, 5.3% had TEAEs leading to treatment discontinuation compared to 3.4% in the placebo group. In TP1, 1 Grade 4 TEAE (preferred term pancreatitis) was reported in the danicopan group and none in the placebo group. There were no Grade 5 events reported in TP1.

In treatment period 2 (TP2, unblinded), 23 patients from the placebo group switched to danicopan and 48 patients in the danicopan group continued on active treatment. The overall incidence of TEAEs in

the 71 patients exposed to danicopan in combination with C5-inhibitors was 62.0%. Six (8.5%) patients (3 in DAN/DAN, 3 in PBO/DAN) had 7 SAEs reported during TP2. There were 7 TEAEs related to liver enzyme abnormalities reported in 6 (8.5%) patients.
There were no TEAEs leading to treatment discontinuation in TP2. No Grade 5 TEAEs were reported in TP2.

Regarding all data of TP1 and TP2 up until the latest data cut-off (20 September 2022), the cumulative incidence of TEAEs was 90.0% in the 80 patients exposed to danicopan as an add-on therapy to C5-inhibitors. Three (3.8%) patients experienced a Grade 4 TEAE. SAEs were reported in 16.3% patients. Please refer to the information for healthcare professionals for details regarding the most frequent adverse reactions.

Pooled safety analyses included 4 studies in participants with PNH (2 as add-on to C5 inhibitors and 2 monotherapy) and 3 studies with danicopan as monotherapy in participants with complement 3 glomerulopathy (C3G)/immune-complex membranoproliferative glomerulonephritis (IC-MPGN), resulting in a safety pool of N=139 patients. The pooled analyses did not suggest a different safety profile from that in study ALXN2040-PNH-301. Please refer to the information for healthcare professionals for further information.

6.5 Final clinical benefit-risk assessment

The add-on treatment with danicopan resulted in a statistically significant and clinically meaningful increase in Hgb from baseline to Week 12 compared with placebo. The safety profile is acceptable, despite the considerable uncertainty that is introduced by the overall small patient numbers and the relatively short observation period. In light of the rarity of the disease and the existing medical need, the final benefit-risk assessment is positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Voydeya was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

VOYDEYA®

Composition

Active substances

Danicopan

Excipients

Tablet core

Lactose monohydrate (50 mg film-coated tablet: 60.5 mg; 100 mg film-coated tablet: 121.0 mg), Microcrystalline cellulose, Croscarmellose sodium, Sodium lauril sulfate, Magnesium stearate, Silica Colloidal Anhydrous, Hypromellose acetate succinate.

Film-coating

Polyvinyl alcohol, Titanium dioxide, Macrogol 3350, Talc.
Total sodium content: 50 mg film-coated tablet: max. 1.22 mg; 100 mg film-coated tablet: max. 2.44 mg

Pharmaceutical form and active substance quantity per unit

Voydeya 50 mg film-coated tablets

White to off-white, round film-coated tablets, “DCN” above “50” debossed on one side, plain on the other side.
Each film-coated tablet contains 50 mg of danicopan.

Voydeya 100 mg film-coated tablets

White to off-white, round film-coated tablets, “DCN” above “100” debossed on one side, plain on the other side.
Each film-coated tablet contains 100 mg of danicopan.

Indications/Uses

Voydeya is used as an add-on to ravulizumab or eculizumab for the treatment of clinically relevant extravascular haemolysis (EVH, as defined in current clinical guidelines) after at least 6 months of monotherapy with a C5 inhibitor in adult patients with paroxysmal nocturnal haemoglobinuria (PNH; see ‘Clinical efficacy’).

Dosage/Administration

Voydeya should be initiated by a healthcare professional experienced in the management of patients with haematological disorders.

Dosage

The recommended starting dose is 150 mg three times a day administered orally, approximately 8 hours apart (± 2 hours). Dose can be increased to 200 mg three times a day after a minimum of 4 weeks of treatment depending on clinical response.
PNH is a chronic disease and add-on treatment with Voydeya is recommended to continue for the patient's lifetime, unless the discontinuation of Voydeya is clinically indicated.
Voydeya must not be administered as monotherapy and should be prescribed as an add-on to ravulizumab or eculizumab.

Discontinuation of treatment

If Voydeya is discontinued, the dose should be tapered over a 6-day period until complete cessation as follows:

- 150 mg regimen: 100 mg three times a day for 3 days, followed by 50 mg three times a day for 3 days.
- 200 mg regimen: 100 mg three times a day for 3 days, followed by 100 mg twice a day for 3 days.

Patients with hepatic disorders

No dose adjustment is required in patients with mild to moderate hepatic impairment (see the "Pharmacokinetics" section).
Studies have not been conducted in patients with severe hepatic impairment, therefore, Voydeya is not recommended in this patient population (see the "Warnings and precautions" section).

Patients with renal disorders

No dose adjustment is required in patients with renal impairment (see the "Pharmacokinetics" section).

Elderly patients

No dose adjustment is required in patients ⩾ 65 years of age.

Children and adolescents

The safety and efficacy of Voydeya in patients under 18 years of age have not yet been demonstrated. No data are available.

Delayed administration

If a dose is missed, advise patients to take it as soon as it is remembered unless it is within 3 hours prior to the next dose in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take 2 or more doses of Voydeya at the same time.

Mode of administration

Voydeya can be taken with or without food (see the “Pharmacokinetics” section).

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see the “Composition”/”Excipients” section).

Do not initiate Voydeya therapy in patients:

- with unresolved *Neisseria meningitidis* infection.
- with unknown history of vaccination or who are not up to date on their meningococcal vaccines as per local guidelines, unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see the “Warnings and precautions” section).

Warnings and precautions

Serious meningococcal infection

Patients receiving complement inhibitor therapy may have increased susceptibility to meningococcal infections (*Neisseria meningitidis*). Patients must be up to date on their meningococcal vaccines according to current national guidelines for vaccination use, prior to receiving the first dose of Voydeya.

Patients who initiate Voydeya treatment less than 2 weeks after receiving a meningococcal vaccine, must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

Patients must be vaccinated against serogroups A, C, Y, and W135 to prevent the commonly pathogenic meningococcal serogroups. Vaccination against serogroup B is also recommended.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

All patients treated with Voydeya should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected, and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and steps should be taken to seek medical care immediately. This information will be provided in the patient information leaflet.

Laboratory tests

Alanine aminotransferase (ALT) elevations have been observed in clinical trials (see the “Undesirable effects” section). It is recommended that liver enzyme tests be performed before treatment begins. Following initiation of treatment, routine chemistry laboratory monitoring as per PNH management is

recommended. Consider treatment interruption or discontinuation if liver enzyme elevations are clinically significant or if patients become symptomatic (for example, in patients who, in the absence of haemolysis, develop persistent elevations in alanine aminotransferase (ALT) ⩾ 5 × ULN or elevations in ALT ⩾ 3 × ULN accompanied by abdominal pain, nausea, vomiting, increased conjugated bilirubin > 2 × ULN, or increased international normalised ratio (INR) > 1.5 × ULN).
Studies have not been conducted in patients with severe hepatic impairment (see the "Dosage/Administration" section).

Excipients
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Interactions

Available nonclinical data showed non-CYP450 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 substrate with high permeability and low efflux ratio *in vitro*, 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. Thus, danicopan is considered to have no or low likelihood to be subject to drug-drug interactions due to inhibition of these drug transporters.
Co administration of ravulizumab or eculizumab does not appear to impact danicopan plasma concentrations.

Effects of active substance danicopan on the pharmacokinetics of other agents
Concomitant use with caution
P-gp substrates
Co-administration of a single oral dose of 180 mg fexofenadine, a P-gp substrate, with 150 mg three times daily doses of danicopan resulted in increased fexofenadine C_{max} and $AUC_{0\text{-}inf}$ by 1.42-fold and 1.62-fold, respectively.
Co-administration of a single oral dose of 2 mg tacrolimus, a P-gp substrate, with 200 mg three times daily doses of danicopan resulted in increased tacrolimus C_{max} and $AUC_{0\text{-}inf}$ by 1.13-fold and 1.49-fold, respectively.

BCRP substrates

Co-administration of a single oral dose of 20 mg rosuvastatin, a BCRP substrate, with 200 mg three times daily doses of danicopan resulted in increase in rosuvastatin C_{max} and $AUC_{0\text{-}inf}$ by 3.29-fold and 2.25-fold, respectively. This result suggests that danicopan is an inhibitor of BCRP.

Table below shows the geometric mean ratios (GMR) for the pharmacokinetic parameters during administration with/without concomitant medication with 90% confidence intervals (CI).

Table: Interactions between the active substance of medicinal product danicopan and other medicinal products

Active substance by therapeutic area (Dosage regimen)	**Effects on drug concentration GMR (90%CI)**	**Recommendation on concomitant use**
Fexofenadine (180 mg single dose) Danicopan (150 mg TID) Tacrolimus (2 mg single dose) Danicopan (200 mg TID)	Fexofenadine: $AUC_{0\text{-}inf}$: 162% (147-179%) C_{max}: 142% (128-159%) Tacrolimus: $AUC_{0\text{-}inf}$: 149% (140-159%) C_{max}: 113% (102-125%) (Inhibition of P-gp)	Caution is needed in co-administering drugs that are known to be substrates of P-gp. If necessary, dose adjustments of P-gp substrates may also be carried out in accordance with the respective information for healthcare professionals.
Rosuvastatin (20 mg single dose) Danicopan (200 mg TID)	Rosuvastatin: $AUC_{0\text{-}inf}$: 225% (205-246%) C_{max}: 329% (276-392%) (Inhibition of BCRP)	Caution is needed in co-administering drugs that are known to be substrates of BCRP. If necessary, dose adjustments of BCRP substrates may also be carried out in accordance with the respective information for healthcare professionals. Since adverse reactions to these drugs may be enhanced, patients should be carefully monitored for the onset of adverse reactions.

Abbreviations: GMR = geometric mean ratio; CI = confidence interval; P-gp = P-glycoprotein; BCRP = Breast cancer resistance protein; C_{max} = maximum plasma concentration; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from zero extrapolated to infinity.

Other interactions

Danicopan is not an inhibitor of CYP1A2, CYP2C8 and CYP2D6. Dedicated clinical pharmacology studies confirmed that no clinically significant drug interactions were observed with danicopan as an inhibitor of other enzymes, i.e. CYP2B6, CYP2C9, CYP2C19, CYP3A4, UGT1A1 and UGT2B7. Danicopan is not an inhibitor of transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K.

Pregnancy, lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception methods during treatment with Voydeya and until 3 days after discontinuation.
As Voydeya is used as add-on to ravulizumab or eculizumab, the corresponding Information for Healthcare Professionals should be consulted with regard to Women of Childbearing Potential (please refer to the Information for Healthcare Professionals for ravulizumab and eculizumab).

Pregnancy

There are no data from the use of danicopan in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see the “Preclinical data” section). As a precautionary measure, it is preferable to avoid the use of Voydeya during pregnancy.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of danicopan/metabolites in milk (see the “Preclinical data” section). A risk to the newborns/infants cannot be excluded. Voydeya should not be used during breastfeeding and breastfeeding should not be initiated until 3 days after treatment discontinuation.

Fertility

No human data on the effect of danicopan on fertility are available. Animal studies do not indicate any potential direct effect on fertility of males or females at therapeutically relevant dose (see the “Preclinical data” section).

Effects on ability to drive and use machines

Voydeya is expected to have no or negligible influence on the ability to drive and use machines.

Undesirable effects

As Voydeya is used as add-on to ravulizumab or eculizumab, the corresponding information for healthcare professionals should be consulted with regard to the undesirable effects associated with ravulizumab or eculizumab (please refer to the information for healthcare professionals for ravulizumab and eculizumab).

Summary of the safety profile

The safety profile of Voydeya is based on ongoing and completed clinical trials in 143 patients who received Voydeya. The most common adverse drug reactions (≥ 10%) across all clinical trials are pyrexia (27%), headache (23%), diarrhoea (17%), nausea (14%), upper respiratory tract infection (13%), fatigue (13%), vomiting (11%), oropharyngeal pain (11%), arthralgia (11%), pain in extremity (11%), anaemia (10%) and hepatic enzyme increased (10%).

List of adverse reactions

In Table 1, adverse reactions with Voydeya are listed by system organ class and preferred term using MedDRA frequency convention "very common" (≥1/10), "common" (≥1/100, <1/10), "uncommon" (≥1/1,000, <1/100), “rare” (≥1/10,000, <1/1,000), and “very rare” (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Tabulated list of adverse reactions from clinical trials[a]

MedDRA System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥1/10,000 to <1/1,000)[d]	Very rare (<1/10,000)[d]
Infections and infestations	Upper respiratory tract infection (13%)[a]	Urinary tract infection[a], Nasopharyngitis[a], Influenza[a], Sinusitis[a], Cystitis[a], Bronchitis[a], Cellulitis[a], Pneumonia[a], Viral infection[a]	Gastrointestinal infection[a], Impetigo[a, b], Oral herpes[a]		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Myelodysplastic syndrome[a]			
Blood and lymphatic system disorders	Anaemia[a] (10 %)	Haemolysis[a], Thrombocytopenia[a], Leukopenia[a] Haemoglobin decreased[a]			
Immune system disorders		Hypersensitivity[a, b]			
Metabolism and nutrition disorder		Decreased appetite[a]			
Psychiatric disorders		Anxiety[a], Depression[a], Insomnia[a]	Abnormal dreams[a, b]		
Nervous system disorders	Headache (23%)	Dizziness[a] Paraesthesia[a], Syncope[a, b]			
Eye disorders		Vision blurred[a,b]			
Ear and labyrinth		Vertigo[a],			

disorders		Tinnitus[a]			
Cardiac disorders		Palpitations[a]			
Vascular disorders		Hypertension[a], Hot flush[a], Hypotension[a,b], Haematoma[a,b]			
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain (11%)[a]	Dyspnoea[a], Nasal congestion[a], Rhinorrhoea[a], Epistaxis[a]			
Gastrointestinal disorders	Diarrhoea (17%)[a], Nausea (14%)[a], Vomiting (11%)[a]	Abdominal pain[a], Constipation[a], Dyspepsia[a], Abdominal distension[a, b]			
Hepatobiliary disorders	Hepatic enzyme increased (10%)[c]	Jaundice[a] Aspartate aminotransferase increased[a]			
Skin and subcutaneous tissue disorders		Pruritus[a], Erythema[a], Rash[a, b], Alopecia[a], Dry skin[a], Hyperhidrosis[a]	Dermatitis[a, b], Urticaria[a]		
Musculoskeletal and connective tissue disorders	Arthralgia (11%)[a], Pain in extremity (11%)[a]	Back pain[a], Muscle spasms[a], Neck pain[a], Bone pain[a]	Joint swelling[a]		
Renal and urinary disorders		Renal impairment[a,b], Haematuria[a]	Dysuria[a]		
General disorders and administration site conditions	Pyrexia (27%)[a], Fatigue (13%)[a]	Chest discomfort[a], Chills[a], Oedema[a], Asthenia[a]			

[a] Part of the safety pool received an add-on therapy with danicopan and a C5 inhibitor.
[b] Identified adverse reaction from other clinical trial experience. This adverse reaction has not been reported in patients with PNH.
[c] Hepatic enzyme increased includes preferred terms alanine aminotransferase increased, hepatic function abnormal, hepatic enzyme increased, and transaminases increased.
[d] No statement possible in this frequency category due to the limited data pool.

Description of specific adverse reactions

Hepatic enzyme increased

In the 12-week randomized control period of Study ALXN2040-PNH-301 (see the "Pharmacodynamics" section), laboratory abnormalities related to elevations in alanine aminotransferase (ALT) levels were observed in 14.0% of patients on Voydeya compared to 3.4% of patients on placebo. In Voydeya-treated patients, ALT elevations > 3 × the upper limit of normal (ULN) and ≤ 5 × ULN occurred in 8.8% of patients and > 5 × ULN and ≤ 10 × ULN in 5.3% of patients. There were no elevations > 10 × ULN. All patients were asymptomatic, and all elevations were transient. Some elevations occurred in the context of haemolysis. Patients with PNH may have elevated hepatic enzymes during haemolysis as part of the natural history and clinical presentation of the disease; patients with high transfusion requirements may also present with hepatic enzyme abnormalities associated with transfused iron and subsequent liver iron overload.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Single doses up to 1,200 mg and multiple doses up to 800 mg twice a day have been taken in healthy volunteers. ALT elevations occurred after treatment cessation without a taper in 2 subjects who received 500 mg and 800 mg twice a day for 14 days. All abnormal ALT findings were transient, with no evidence of hepatic function abnormality and resolved spontaneously.
In case of overdose, elevations in aminotransferase and other liver parameters may occur. General supportive measures are recommended. It is not known whether danicopan can be removed by dialysis.

Properties/Effects

ATC code

L04AJ09

Mechanism of action

Danicopan binds reversibly to complement factor D and acts as a selective inhibitor of FD function. By inhibiting FD, danicopan blocks the activation of complement alternative pathway (AP) and the production of multiple effectors, that include C3 fragments. The deposition of C3 fragments on red

blood cells is a key cause of the EVH which can become clinically significant in a small subset of patients with PNH on a complement component 5 (C5) inhibitor.

Pharmacodynamics

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 (RBCs).

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*.

In patients with PNH and clinically significant EVH treated with danicopan (Voydeya) at doses ranging from 100 mg three times a day to 200 mg three times a day, administered with an existing regimen of ravulizumab or eculizumab treatment, results showed inhibition of AP activity. The plasma Bb level, an in vivo biomarker for FD inhibition, was reduced from baseline after adding danicopan (Voydeya). Moreover, the fraction of circulating PNH red blood cells with measured C3 fragment deposition was notably decreased by treatment with danicopan (Voydeya).

Cardiac electrophysiology

Single oral doses of danicopan administered at 400 mg, 800 mg, or 1,200 mg did not prolong QTc interval. There were no categorical alerts of concern regarding electrocardiogram intervals or wave form abnormalities.

Clinical efficacy

The efficacy and safety of danicopan (Voydeya) as an add-on to ravulizumab or eculizumab in adult patients with PNH who have clinically relevant EVH were assessed in a multiple-region, randomised, double-blind, placebo-controlled, phase 3 study (ALXN2040-PNH-301). The study enrolled 86 patients with PNH who had been treated with a stable dose of ravulizumab or eculizumab for at least the previous 6 months and had anaemia (haemoglobin [Hgb] ≤ 9.5 g/dL) with absolute reticulocyte count ≥ 120 × 10^9/L with or without transfusion support.

Danicopan (Voydeya) was administered in accordance with the recommended dosing described in the “Dosage/Administration” section (150 mg three times a day, and up to a maximum of 200 mg three times a day depending on the clinical response).

Patients were evaluated for history of vaccination and had to be vaccinated against meningococcal infection prior to or at the time of initiating treatment with danicopan (Voydeya) if vaccination status within 3 years could not verified.

Patients were randomised to danicopan (Voydeya) or placebo three times a day in a 2:1 ratio for 12 weeks in addition to background ravulizumab or eculizumab treatment in both groups. After Week 12, all patients received danicopan (Voydeya) as an add-on to their background ravulizumab or eculizumab treatment up to Week 24. At the end of the treatment periods (Week 24), patients were offered to enter a Long-Term Extension (LTE) Period and continued to receive danicopan (Voydeya) with background ravulizumab or eculizumab.

Demographic or baseline characteristics were generally balanced between treatment groups. PNH medical history was similar between the danicopan (Voydeya) treatment group and the placebo control group. The mean age at baseline was 52.8 years and the majority of patients were female (62.8%). Mean haemoglobin levels at baseline were 7.75 g/dL [4.81 mmol/L] and mean reticulocyte counts were 239.40 × 10^9/L. Within 24 weeks prior to the first dose, 76 patients (88.4%) had pRBC/whole blood transfusions and the mean number of transfusion instances was 2.6. LDH levels were 298.13 U/L and FACIT-Fatigue scores were 33.24. The study enrolled 51 patients (59.3%) on ravulizumab and 35 patients (40.7%) on eculizumab.

The primary endpoint was the change in Hgb level from Baseline to Week 12. Key secondary endpoints were the proportion of patients with Hgb increase of ≥ 2 g/dL [1.2 mmol/L] at Week 12 in the absence of transfusions, the proportion of patients with transfusion avoidance through Week 12, the change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores at Week 12, and change from Baseline in absolute reticulocyte count at Week 12. Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol specified guidelines for transfusion from Baseline through 12 Week Treatment Period 1.

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 (Voydeya) as an add-on to ravulizumab or eculizumab was superior to placebo as an add-on to ravulizumab or eculizumab and resulted in a statistically significant and clinically meaningful increase in Hgb from Baseline to Week 12. The least squares (LS) mean (standard error [SE]) increase in Hgb was 2.94 (0.211) g/dL in the danicopan (Voydeya) group compared with 0.50 (0.313) g/dL in the placebo group. The treatment group difference was 2.44 (0.375) g/dL ($p < 0.0001$) (see Table 2). A statistically significant difference was observed as early as Week 1 and a clinically meaningful effect on Hgb was seen as early as Week 2.

Danicopan (Voydeya) also achieved statistically significant improvement compared to placebo for all 4 key secondary endpoints (Table 2).

Supplemental results at week 12 based on all randomised patients (N = 86) are consistent with those from the primary efficacy analysis (N = 63).

During the 12-week treatment period 1, 14 of 57 (24.6%) patients in the danicopan (Voydeya) add-on group were dose escalated from 150 mg to 200 mg three times a day. Four patients (2 randomised to danicopan (Voydeya) and 2 randomised to placebo) discontinued treatment during treatment period 1. There were no discontinuations due to haemolysis.

Table 2: Analysis of primary and key secondary endpoints at week 12

	Voydeya (add-on with ravulizumab or eculizumab) N = 42	**Placebo (add-on with ravulizumab or eculizumab) N = 21**
Change in haemoglobin level (primary endpoint)		
Mean change from Baseline to Week 12 (g/dL [mmol/L)	2.94	0.50
Treatment difference* (95% CI)	2.44 (95% CI: 1.69, 3.20)	
P-value	< 0.0001	
Proportion of patients with haemoglobin increase of ≥ 2 g/dL [1.2 mmol/L] in the absence of transfusion		
At Week 12 (%)	59.5	0
Treatment difference** (95% CI)	46.9 (95% CI: 29.2, 64.7)	
P-value	< 0.0001	
Proportion of patients with transfusion avoidance		
Through 12-Week treatment period (%)	83.3	38.1
Treatment difference** (95% CI)	41.7 (95% CI: 22.7, 60.8)	
P-value**	0.0004	
Change in FACIT-Fatigue score		
Mean change from Baseline to Week 12	7.97	1.85
Treatment difference* (95% CI)	6.12 (95% CI: 2.33, 9.91)	
P-value*	0.0021	
Change in absolute reticulocyte count		
Mean change from Baseline to Week 12 (10^9/L)	-83.8	3.5
Treatment difference* (95% CI)	-87.2 (95% CI: -117.7, -56.7)	
P-value*	< 0.0001	

* Based on mixed-effect model for repeated measures.
** Difference in rates and associated 95% CI are calculated using Miettinen and Nurminen method adjusting for stratification factors. P-value is based on Cochrane-Mantel-Haenszel test.
Abbreviations: CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; MMRM = mixed-effect model for repeated measures

The results at Week 24 were consistent with those at Week 12 and support maintenance of the effect. Among the 55 patients with PNH who received danicopan (Voydeya) for 24 weeks, the LS mean change in Hgb from Baseline at Week 24 was 2.95 g/dL [1.83 mmol/L] (95% CI: 2.42 [1.50], 3.48 [2.16]).

Efficacy results up to week 72 are consistent with those at week 12 and week 24. In patients who received danicopan (Voydeya) for 72 weeks (N = 16) the mean change in Hgb from baseline to week 72 was 2.99 g/dL [1.86 mmol/L].

Pharmacokinetics

Absorption

Danicopan is well absorbed and the maximum plasma concentration is reached at about 3 hours after oral dosing. Danicopan exposure is dose proportional over the dose range of 150 to 200 mg. Steady-state conditions are reached approximately on Day 2 after dosing with no accumulation at the 200 mg dose. When the danicopan tablet was administered with a high-fat meal, AUC and C_{max} observed after drug administration were approximately 25%, and 93% higher, respectively, compared to the fasted state. Median T_{max} was comparable when danicopan was administered in the fed or fasted state at approximately 3.0 and 2.5 hours, respectively. These changes are not considered to be clinically meaningful (see the “Dosage/Administration” section).

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 $AUC_{0\text{-}inf}$ of 0.545. Danicopan plasma concentrations appeared to decline in a biphasic manner after T_{max}. The estimated oral apparent volume of distribution for a 75 kg person using the population-PK model was 165 L for Vc/F and 232 L for Vp/F (397 L total), suggesting a moderate distribution of danicopan to peripheral tissue.

Metabolism

Danicopan is extensively metabolized (96%) after oral dosing via oxidation, reduction, and hydrolysis pathways, with amide hydrolysis identified as the major pathway of elimination. Metabolism by CYP mediated mechanisms is minimal.

Elimination

Following oral administration, the principal route of elimination is in the faeces (approximately 69% of the administered dose, compared to approximately 25% of the administered dose in urine). In the population pharmacokinetic (PK) analysis in patients with PNH who have clinically significant EVH, the $t_{½}$ had an estimated mean value of 7.88 hours and with a range from 4.3 to 12.2 hours and the oral CL/F was estimated at 79.5 L/hr.

Kinetics in specific patient groups

No clinically significant differences in the pharmacokinetics of danicopan were observed based on sex, age (16.9 to 82 years), or race based on population PK assessment.

Hepatic impairment

No significant difference in danicopan exposure is observed in subjects with moderate hepatic impairment (Child-Pugh Class B) as compared to subjects with normal hepatic function (see the "Dosage/Administration" section). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Renal impairment

Following oral administration of danicopan 200 mg in subjects with severe renal impairment (creatinine clearance [CL] < 30 mL/min), the total danicopan exposure (AUC) increased by approximately 50% as compared to subjects with normal renal function. There was no clinically meaningful change in C_{max}, T_{max}, and $t_{½}$. Renal excretion is not the major route for clearing danicopan from the body, even in subjects with normal renal function (see the "Dosage/Administration" section).

Preclinical data

A reversible hepatobiliary cholestasis with a safety margin of 5 relative to clinical exposure at 200 mg TID was observed in dogs.

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.

Carcinogenicity

Danicopan was not carcinogenic in the 6-month carcinogenicity study in TgRasH2 mice and 2-year carcinogenicity study in Wistar Han rats. Exposure multiples at NOAELs in these studies relative to the human exposure at the 200 mg three times a day (TID) dose were ~39-77-fold in TgRasH2 mice and ~15-23 fold in WH rats, respectively.

Impairment of fertility

In a rabbit study, no effects were noted in the male and female fertility and copulation/conception indices at 250 mg/kg/day NOAEL at exposures ~8-fold above the human exposure.
The top dose of 500 mg/kg/day was not tolerated well and danicopan-related toxicities were apparent at doses ⩾250 mg/kg/day for males and at 500 mg/kg/day for females. These were evidenced by adverse mean body weight losses and lower mean body weight gains, with corresponding lower mean body weights, reduced mean food consumption, and decreased defecation. The severity of these effects resulted in mortality and/or moribundity at these dose levels. Based on these results, the NOAEL for systemic toxicity was considered to be 125 mg/kg/day for males and 250 mg/kg/day for females. Based on poor male and female reproductive performance, likely secondary to poor tolerability at 500 mg/kg/day, the NOAEL for male and female reproductive toxicity was considered to be 250 mg/kg/day. There were no test article-related effects on intrauterine survival at any dosage

level. Therefore, a dosage level of 500 mg/kg/day (the highest dosage level tested) was considered to be the NOAEL for early embryonic toxicity.

Reproductive toxicity

There were no effects on early embryonic development and foetal development and during post-natal development in rabbits up to mean maternal systemic exposure ~18-fold above human exposure (500 mg/kg/day) or during post-natal development (250 mg/kg/day). In the rats, there were no effects on embryo-foetal development up to maternal exposure ~28-fold above the human exposure at 200 mg three times a day at the 1000 mg/kg/day dose.

Other data

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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after first opening (only for the bottles pack)

Use within 48 days after opening.

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.

Authorisation number

69301 (Swissmedic)

Packs

Voydeya 50 mg + 100 mg film-coated tablets in blisters
Each pack contains 4 blister wallet cards, each containing 21 film-coated tablets of 50 mg and 21 film-coated tablets of 100 mg (A)
Voydeya 100 mg film-coated tablets in blisters
Each pack contains 4 blister wallet cards, each containing 42 film-coated tablets of 100 mg (A)
Voydeya 50 mg + 100 mg film-coated tablets in bottles

Each pack contains 1 bottle of 90 film coated tablets of 50 mg and 1 bottle of 90 film-coated tablets of 100 mg (A)

Voydeya 100 mg film-coated tablets in bottles

Each pack contains 2 bottles of 90 film coated tablets of 100 mg (A)

Marketing authorisation holder

Alexion Pharma GmbH

Neuhofstrasse 34, 6340 Baar

Date of revision of the text

November 2023