swissmedic

Date: 30 June 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Dawnzera

International non-proprietary name:	donidalorsen
Pharmaceutical form:	Solution for injection in pre-filled pen
Dosage strength(s):	Each pre-filled pen contains 80 mg donidalorsen (equivalent to 84 mg donidalorsen sodium) in 0.8 mL of solution
Route(s) of administration:	Subcutaneous injection
Marketing authorisation holder:	Otsuka Pharmaceutical
Marketing authorisation no.:	69883
Decision and decision date:	approved on 2 June 2026

Note:

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

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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
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
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
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
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
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) and information regarding procedure

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

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 1 TPA.
Orphan drug status was granted on 22.05.2024.

2.2 Indication and dosage

2.2.1 Requested indication

Dawnzera is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

2.2.2 Approved indication

Dawnzera is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended starting dose in adult and adolescent patients is 80 mg donidalorsen by subcutaneous injection. Doses should be administered once monthly.
A dosing interval of 80 mg once every 2 months may be considered if the patient is well controlled (e.g., attack free) for at least 3 months while receiving Dawnzera.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	12 March 2025
Formal control completed	18 March 2025
List of Questions (LoQ)	16 July 2025
Response to LoQ	13 October 2025
Preliminary decision	9 January 2026
Response to preliminary decision	5 March 2026
Final decision	2 June 2026
Decision	approval

3 Medical context

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterised by deficiency of C1 inhibitor; the C1 inhibitor may be truly deficient due to genetic mutations (type I HAE) or dysfunctional (type II HAE). More than 150 mutations have been identified. The disorder is characterised by disabling recurrent episodes of local skin swellings, painful abdominal attacks, and, occasionally, laryngeal attacks that can be life-threatening.
Estimates of HAE prevalence range from 1 in 150,000 to 1 in 10,000, but most studies report prevalence as 1 in 50,000-60,000. Roche et al. (2005) assessed the prevalence of HAE in Spain in July 1999 and reported 1.09 cases per 100,000 population. The mean age of onset of symptoms was 12.6 years with a mean age of diagnosis of 24.9 years, suggesting a significant delay in the diagnosis of HAE. Another study in Norway reported the prevalence of HAE to be 1.75 cases per 100,000 population.
Hereditary angioedema typically first appears during childhood or adolescence and then persists throughout life. A study by Bork et al. (2006) reported a mean age of onset of 11.2 years, and 64/209 (30%) patients with HAE had disease onset by age 5.
Patients with HAE are generally healthy apart from their HAE. However, HAE may be associated with autoimmune diseases. In particular, systemic lupus erythematosus (SLE) has been reported in association with HAE. In one study of 157 patients with HAE, 19 (12%) had an autoimmune disorder such as inflammatory bowel disease, Sjogren's syndrome, lupus, or glomerulonephritis.
Treatment for HAE has two aspects. Some interventions seek to terminate acute attacks; others involve drugs whose goal is prophylaxis against future attacks. In the past, antihistamines, corticosteroids and epinephrine were utilised for acute attacks, despite a lack of evidence that they were effective, but there were no HAE-specific treatments then. Since 2008, various forms of C1 inhibitor have become available. Two randomised placebo-controlled trials demonstrated the efficacy of Cinryze, a C1 inhibitor (human) concentrate which is now approved in Europe. Other similar agents, including ecallantide and icatibant, are FDA-approved and available in the US for acute attacks. Icatibant is also approved in the EU and in Switzerland.
For long-term prophylaxis, androgens have been utilised in the past under the rationale that they stimulate the production of C1 inhibitor. However, although they are effective in the prevention of attacks, it is generally believed that their toxicity limits their utility for long-term use. Antifibrinolytics, such as tranexamic acid, have also been utilised for this purpose, but careful studies have not clearly demonstrated efficacy. Lanadelumab and berotralstat, kallikrein inhibitors, are available for use as prophylactic agents.

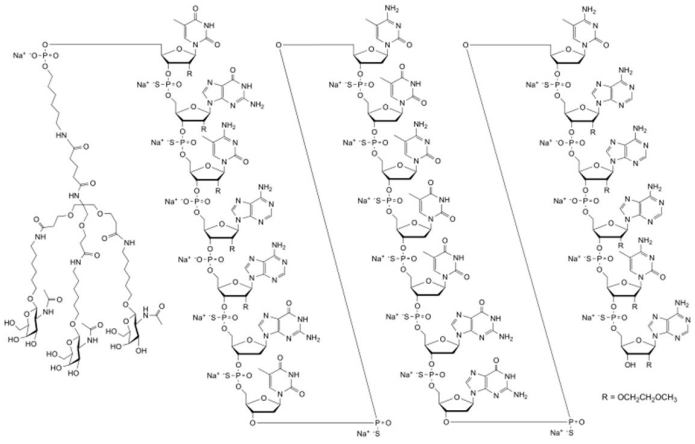
4 Quality aspects

4.1 Drug substance

INN:	Donidalorsen
Molecular mass:	8672.7 Da (free acid)
	9112.3 Da (sodium salt)

Donidalorsen sodium drug substance is a synthetic antisense oligonucleotide (ASO) with 20 base residues.

Molecular structure:



Manufacture

The drug substance is manufactured by solid-phase synthesis using well defined and characterised starting materials. The ASO is covalently bonded to the trivalent N-acetylgalactosamine (GalNAc), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR), to form an ASO-GalNAc conjugate.

The synthesis and purification of the drug substance are described in sufficient detail, including a clear flow diagram and a narrative description of each step, and appropriate in-process controls are applied.

Specification and Analytical Procedures

In order to ensure a consistent quality of donidalorsen sodium, the specifications include all relevant test parameters. Acceptance criteria are based on the results of release and stability studies on development and commercial batches and supported by toxicological studies.

Detailed information on the analytical procedures and method validation reports have been provided. Impurities in the drug substance have been adequately discussed.

Container Closure System

The lyophilised bulk drug substance is packaged in HDPE bottles.

Stability

Appropriate stability data have been presented. Based on the results, a satisfactory storage condition and retest period were established.

4.2 Drug product

Description and composition

The formulation of donidalorsen solution for injection contains 100 mg/mL free acid (105 mg/mL donidalorsen sodium) in sodium phosphate buffer, at pH 7.4. Sodium chloride is added to achieve an isotonic solution for SC administration.

Donidalorsen solution for injection, 80 mg, is a sterile, preservative-free solution.

The solution appears clear and colourless to yellow.

The drug product is provided in a glass prefilled syringe (PFS), which is assembled into an autoinjector for subcutaneous (SC) administration with a deliverable volume of 0.8 mL.

Manufacture

The drug product manufacturing process consists of dissolving the drug substance in an appropriate buffer, sterile filtration, and aseptic filling into syringes, followed by autoinjector assembly and packaging. The manufacturing process is described in sufficient detail, including a flow diagram and narrative of each step and is considered adequate. The process is sufficiently validated, and appropriate in-process controls are performed.

Container Closure System

Donidalorsen solution for injection is filled into a sterile syringe with 0.8 mL deliverable volume, which is further assembled into an autoinjector for the final drug product presentation.

Specification and Analytical Procedures

Drug product release specifications have been defined based on the characteristics of the drug substance and the drug product, compendial requirements for the dosage form and requirements for the functionality of the autoinjector. Results of release testing and stability studies of development and commercial batches were submitted in order to demonstrate consistent quality and to justify the acceptance criteria.

The analytical methods used have been adequately described and appropriately validated.

Stability

The product is stable for the proposed shelf life under the approved storage conditions, as demonstrated by the provided stability data of development and commercial batches.

4.3 Quality conclusions

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

5 Nonclinical aspects

5.1 Pharmacology

Primary Pharmacodynamics
Hereditary angioedema (HAE) is a rare and potentially life-threatening autosomal dominant inherited disease leading to inadvertent vascular permeability. It is often caused by mutations in the complement 1 inhibitor gene (C1-INH), resulting in uncontrolled activation of plasma prekallikrein (PKK) and subsequent formation of bradykinin.

Donidalorsen (ISIS 721744), is a GalNAc3-linker conjugated chemically modified (2'-MOE, PS, among others) 20-nucleotide antisense oligonucleotide (ASO), specifically designed to degrade PKK mRNA via RNase H1 activation. Donidalorsen and several variants were tested *in vitro* in cultured hepatocellular carcinoma cells and primary human hepatocytes, and *in vivo* in mice and monkeys. Donidalorsen is not pharmacologically active in the mouse due to sequence differences between the human and the mouse PKK mRNA. The *in vivo* pharmacodynamics of donidalorsen was investigated in transgenic mice expressing the human PKK gene or in wild-type C57BL/6J mice with an unconjugated mouse surrogate ASO. Donidalorsen was shown to efficiently downregulate PKK mRNA in human cells and, after subcutaneous (SC) injection, in human-PKK transgenic mice and monkeys. The GalNAc3 modification increased the potency of uptake of the ASO by hepatocytes by 46-fold in cells in culture and by about 10-fold in mice. In monkeys, donidalorsen doses of 6, 12 and 30 mg/kg/wk resulted in 58%, 60% and 62% reductions, respectively, in hepatic PKK mRNA levels. PKK plasma protein activity was also dose-dependently reduced by 75%, 79% and 87% at 2, 6, and 12 mg/kg/wk, respectively. Both PKK liver mRNA expression and plasma protein activity levels were completely restored after a 26-week recovery period. In mice, it was shown that experimentally induced vascular permeability was decreased by mouse-PKK-specific surrogate ASOs. The provided off-target analyses and proof-of-concept can be accepted.

Safety Pharmacology
In vitro, the hERG assay was used to assess the potential of donidalorsen to induce prolongation of the QT interval. Donidalorsen did not exhibit statistically significant hERG inhibition when compared to the vehicle at concentrations up to 300 µM.

In vivo, a single administration of donidalorsen was used to evaluate potential effects on cardiovascular, respiratory, and central nervous system (CNS) function in monkeys. No critical effects on cardiovascular, respiratory or neurobehavioural parameters were identified after SC administration of donidalorsen at 12 or 30 mg/kg.

Pharmacodynamic Drug Interactions
No dedicated pharmacodynamic studies have been performed. However, donidalorsen interference with warfarin and ibuprofen plasma protein binding was investigated. Donidalorsen is highly bound (≥ 96%) to plasma proteins. The protein binding affinity is relatively weak. No drug-drug interaction with regards to plasma protein binding between donidalorsen and warfarin and ibuprofen were noted.

5.2 Pharmacokinetics

Absorption
Donidalorsen was rapidly absorbed in mice and monkeys after SC administration, with a T_{max} of 1–2 hours. Plasma donidalorsen concentrations declined in a multiphasic manner with a rapid distribution phase, followed by a slower elimination phase with mean half-life values ranging from approximately 2 to 5 weeks in monkeys. Plasma PK was unaltered after repeated dosing for up to 39 weeks in monkeys. Plasma trough concentrations were shown to be in equilibrium with tissues.

Distribution
In mice, liver and kidney are the main organs of donidalorsen accumulation. Liver and kidney concentrations increased with increasing dose. There was no tendency to accumulate in tissues over time. After a 13-week recovery period, donidalorsen decreased below the limit of quantitation. In studies with respect to reproductive toxicity, donidalorsen was below the limit of quantitation in placenta samples, foetal liver samples and in breast milk from lactating parental females.
In rats, radioactively labelled donidalorsen distributed to many tissues. Radioactivity in the kidney was primarily associated with the cortex. There was no notable gender difference. At the 2 mg/kg dose level, T_{max} in the liver was 24 hours and in the kidney 158 hours. At the 10 mg/kg dose level, T_{max} was 8 hours in the liver and around 48 hours for at least half of the analysed tissues.
In monkeys, data from toxicokinetic evaluations showed that donidalorsen distributed extensively to kidney cortex and liver. Unconjugated donidalorsen concentrations were dose-proportional in kidney cortex, while less than dose-proportional in liver, suggesting saturation of liver uptake at higher dose levels. Tissue concentrations decreased in a monophasic pattern. The half-life for a 2 mg/kg dose level in the kidney cortex was 18.6 days and in the liver 12.1 days, and was generally comparable to the estimated plasma elimination half-life (14.1 days).

Metabolism
Unconjugated donidalorsen was the major species of full-length oligonucleotide present in kidney and liver samples at the analysed time points. In mice, unconjugated donidalorsen accounted for approximately 93.1% and 96.4% of the total oligonucleotides present on Day 93. Numerous shortmer oligonucleotide metabolites of unconjugated donidalorsen were evident in the examined samples. The overall metabolic pathways for the oligonucleotide-related metabolites of donidalorsen observed across species is consistent with the endo- and exonuclease-mediated hydrolysis of the deoxyphosphorothioate linkages to form chain-shortened metabolites in tissues which are rapidly excreted in urine. The THA-linker-related metabolism is generally similar across species, with the formation of oxidative metabolites that are eliminated through urine and bile.

Excretion
In mice, donidalorsen and its unconjugated full-length oligonucleotide metabolite were the major components in urine samples. Metabolites generated by endonuclease and exonuclease cleavage were also identified.
In rats, excretion of radioactively labelled donidalorsen occurred via the faecal and urinary routes. Within 48 hours, around 14% of the dose was excreted, with a mean of 1.5% of the dose recovered in urine, and around 12% in faeces. Overall, around 58% of the dose was excreted in faeces and 17% in urine.
In urine samples of monkeys, donidalorsen and unconjugated donidalorsen were the major components. Other metabolites detected in urine from monkeys were 3′-deletion chain-shortened metabolites of donidalorsen with -2 and -3 GalNAc sugar deletions, as well as metabolites of unconjugated donidalorsen with loss of nucleotides from both the 3′- and 5′-ends.

The analysis of the excretion of the THA-linker and its metabolites identified 10 metabolites in mice and monkeys in urine and faeces. The concentrations of the quantifiable metabolites M8 and M12 were substantially higher in monkey faeces than in both plasma (> 1000x) and urine (> 5x). Therefore, faeces is the major route of elimination for the linker-related metabolites.

Pharmacokinetic Drug Interactions
Treatment of cryopreserved human primary hepatocytes with donidalorsen did not cause inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 enzyme activity. With respect to transporters, donidalorsen (at 100 µM) did not inhibit more than 50% of human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, and BSEP transporters, and no effects were noted at lower concentrations.

The M8 linker metabolite was found to inhibit CYP2B6, CYP2C9, CYP2C19 and CYP3A4 at 100 µM in human liver microsomes. CYP3A4 may be able to metabolise the M8 compound, the consumption was slow and produced metabolites that could only be detected at high incubation concentrations. The M8 metabolite was also tested for interaction / interference with human transporters. M8 inhibited MATE1 with an IC_{50} value of 62.7 µM. In the substrate study it was found that M8 is a substrate for OATP1B3. In addition, in BSEP vesicles supplied with ATP compared to the counterpart supplied with AMP, M8 uptake was 4.32-fold, suggesting that M8 is a substrate for BSEP as well. Based on the expected concentrations in human tissue, a safety margin of around 8-fold was calculated by the applicant, and no critical pharmacokinetic drug interactions are expected.

5.3 Toxicology

The nonclinical toxicology studies included 13- and 26-week repeat dose studies in the CD-1 mouse, and 13- and 39-week studies in the cynomolgus monkey. A battery of genotoxicity testing, a 27-week carcinogenicity study in Tg.rasH2 mice and a 2-year carcinogenicity study in rats were performed. In addition, a combined fertility and early embryonic development / embryo-foetal development study and a pre- and postnatal study were performed in mice. A 13-week impurity qualification study was performed in mice. A repeat-dose toxicity study in juvenile mice was performed to support a potential expansion of the indication to paediatric patients between 2 and < 12 years of age.

The main findings in mice at high dose levels were increased liver weights with signs of liver toxicity (increased ALT, AST, ALP blood levels, hepatocyte hypertrophy, necrosis, increased mitotic rates), increased spleen weights and inguinal lymph node enlargements. Liver hepatocytes, Kupffer cells and macrophages displayed vacuolated / granular staining due to the extensive uptake of donidalorsen. Accumulation of vacuolated / granular macrophages was observed in several tissues, including injection sites. Effects in kidneys were limited to the accumulation of basophilic granules in proximal tubular epithelial cells. These effects were reversible or showed signs of reversibility. No toxicological finding related to PKK mRNA knockdown was observed. The NOAEL in mice was defined as 12 mg/kg/q2w.

The main findings in monkeys at 12 and 30 mg/kg/week donidalorsen dose levels were severe, but manageable, PLT reduction events in two animals, reversible increases in CRP, transient prolongation of aPTT and elevated levels of the complement factor Bb. Additional findings were injection site reactions (ISRs) (all groups), increased liver weight with associated hepatocyte hypertrophy, basophilic granules in hepatocytes and Kupffer cells), increased kidney weights with accumulation of basophilic granules within tubular epithelial cells, reactions in mesenteric / mandibular lymph nodes, and perivascular/vascular inflammations in several tissues. The findings reversed or showed signs of reversibility. No toxicological finding related to PKK mRNA knockdown was noted. In the keyhole limpet haemocyanin (KLH) antigenic challenge, donidalorsen was associated with decreases in mean anti-KLH IgM at 6 and 12 mg/kg/week. Anti-donidalorsen antibodies were noted in the toxicity studies, although these did not seem to have any effects on tissue exposure levels. The NOAEL in monkeys was considered as 6 mg/kg/week.

No critical findings were noted in the assessments regarding genotoxicity (Ames test, chromosome aberration assay, *in vivo* mammalian micronucleus assay), reproductive and development toxicity in mice, pre- and postnatal development in mice, SC treatment of juvenile mice with donidalorsen and impurity qualification.

No carcinoma development was observed in a 6-month carcinogenicity study in Tg.ras2 transgenic mice or in a 2-year carcinogenicity study in rats. Hepatocellular adenomas were present in two out of 25 males at 20 mg/kg/q2w. In the 26-week repeat dose study in CD-1 mice, liver adenoma development was also observed in two male animals (at 1 and 12 mg/kg dose levels). In both studies the incidence of hepatocellular adenomas in donidalorsen-treated animals was close to historical

control data and did not show dose-dependence. Of note, mice are more sensitive to liver reactions than other species after repeated treatment with GalNAc3-linker conjugated ASOs.

5.4 Nonclinical conclusions

The nonclinical data showed that SC administered GalNAc3-linker conjugated donidalorsen was selectively taken up by hepatocytes and efficiently downregulated PKK mRNA, resulting in decreased vascular permeability. Safety pharmacology assessments did not reveal critical cardiovascular, respiratory, or CNS effects. No drug-drug interaction with regards to plasma protein binding between donidalorsen and other highly plasma protein bound drugs are expected.

The pharmacokinetic assessment of donidalorsen showed the expected profile of GalNAc3-linker conjugated chemically modified ASOs with rapid absorption after SC administration, rapid distribution to many tissues and an elimination phase of 2-5 weeks. As expected, the main tissues of donidalorsen accumulation are the liver and the kidney. No measurable donidalorsen concentrations were noted in placenta, breast milk and foetal liver samples, suggesting no distribution to offspring. The metabolic pathway of the oligonucleotide part is consistent with the endo- and exonuclease-mediated hydrolysis and excretion via the faecal and urinary routes. Several THA-linker metabolites were identified in urine and faeces. Faeces is the major route of elimination for the linker-related metabolites. Pharmacokinetic drug interaction studies did not show critical effects on a battery of CYP enzymes and human transporters within a safety margin of around 8-fold as compared to the clinical relevant exposure.

The nonclinical toxicological profile of repeat dose treatment with donidalorsen showed an acceptable safety profile. During clinical treatment, PLT events, liver and kidney parameters need to be monitored. The identified NOAELs allow safety margins of up to 29-fold in monkeys (cumulative exposures) and up to 5-fold in mice (cumulative exposures) with respect to the clinical dose of 80 mg donidalorsen. These are acceptable ranges, although the safety margin as calculated in mice is relatively low.

No carcinoma development was observed in a 6-month carcinogenicity study in Tg.ras2 transgenic mice and in a 2-year carcinogenicity study in rats. Hepatocellular adenomas were present in a few male mice. The incidence rates are close to historical control data and do not show dose-dependence. In addition, it can be accepted that mice are known to be sensitive to liver reactions after repeated treatment with GalNAc3-linker conjugated ASOs. Therefore, the overall weight of evidence, including low and variable incidence, lack of dose-response, benign histopathology, alignment with historical control data, no neoplastic findings in the 2-year rat study, and lack of translation to non-rodent species, the observed liver adenomas in mice are not considered indicative of a human carcinogenic risk.

No critical findings were noted in the assessments regarding genotoxicity (Ames test, chromosome aberration assay, *in vivo* mammalian micronucleus assay), reproductive and development toxicity in mice, pre- and postnatal development in mice, SC treatment of juvenile mice with donidalorsen and impurity qualification.

Overall, in can be concluded that the nonclinical assessment of donidalorsen is complete and the benefit outweighs the risk. From the nonclinical perspective, donidalorsen can be approved for the treatment of HAE.

6 Clinical aspects

6.1 Clinical pharmacology

Bioanalytics
Donidalorsen was quantified in human plasma with a validated hybridisation ECL method. The method detects the total full-length ASO, independently of the constitution of the GalNAc conjugate. Around C_{max} at steady state, the relative abundance of intact donidalorsen was found to be 94.5% of the total full-length ASO, whereas the full-length ASO with one, two or three GalNAc sugar moiety deletions, corresponding to 3.7%, 1.2% and 0.6%, respectively, of the relative abundance. Thus, the donidalorsen plasma concentration measured by the ECL method predominantly consists of the conjugated ASO species.

Biopharmaceutical development
The clinical formulation used during clinical development was a 100 mg/mL donidalorsen solution filled into vials and administered subcutaneously by a disposable dosing syringe. The commercial formulation is an autoinjector comprised of a glass prefilled syringe (PFS) assembled into a single-use autoinjector. Bioequivalence (BE) between the two formulations was demonstrated.

Pharmacokinetics
The pharmacokinetics of donidalorsen was analysed using a PopPK model with healthy volunteer and patient data. The final model was a two-compartment model with a biphasic elimination rate.

Absorption
After SC administration, donidalorsen was rapidly absorbed into the systemic circulation, with a T_{max} at approximately 1-3 hours post dose. The accumulation of donidalorsen is negligible.

Distribution
Donidalorsen is highly bound to plasma proteins, independently of the concentrations tested. Approx 98% of donidalorsen was bound to human plasma proteins over the range of concentrations tested. The distribution of donidalorsen was assessed *in vivo* in the non-clinical evaluation. After SC administration, donidalorsen is predominantly distributed to liver and kidney.

Metabolism
The GalNAc-conjugated ASO consists of two different parts undergoing different metabolic pathways. The ASO moiety is cleaved by exo- and endonucleases, whereas the GalNAc linker is cleaved by hydrolysis and is further oxidated.

The unconjugated full-length ASO is the active principle of the molecule. After endocytosis into hepatocytes, a fast hydrolysis of the linker by glycosidases can be assumed. This is supported by non-clinical data from toxicology studies in cynomolgus monkeys, where predominantly the unconjugated ASO was found in liver tissue. The unconjugated ASO undergoes metabolism by endonucleases and exonucleases, leading to shortmers. The shortmers are then further eliminated through renal clearance. The metabolites were analysed in mouse, monkey and human urine, and a similar biotransformation was found across species. The predominant human metabolites in urine were the unconjugated full-length ASO (20-mer), accounting for approx. 40 % of the relative metabolites found in urine, and 5'-shortmers (9 to14-mers) thereof, accounting for less than 10% each. In plasma, no shortmers could be identified.

The metabolic pathway of the linker was assessed in mice, monkey and human plasma samples by MS/MS. M8 and M12 were the predominant linker metabolites found in monkey and human plasma samples, corresponding to approx. 1.5% of the parent concentration.

Elimination
Donidalorsen shows a biphasic elimination phase in plasma. The first elimination phase is attributed to a fast distribution of the donidalorsen into tissues (predominantly into liver and kidney). After 24 hours the majority of donidalorsen is no longer available in plasma.
The population estimate of the terminal elimination half-life of donidalorsen in a typical HAE patient is 31.4 days (approximately 1 month). This parameter is of low clinical relevance, since the terminal half-life likely represents the unconjugated full-length ASO. The slowly formed fragmented oligonucleotide metabolites were subsequently excreted in urine. A strong biliary excretion of linker derived metabolites is seen in nonclinical analysis.

Special populations / Intrinsic factors

Body weight
The body weight (BW) has an effect on the exposure of donidalorsen, with higher BW leading to lower exposure The BW effect was estimated in the PopPK model and was included as a factor on Cl/f, Vc/F, Q/F, and Vp/F. A similar response rate in efficacy can be expected across the investigated BW range.
Due to the BW-dependent exposure, it can be expected that plasma exposure levels above the studied range are reached in patients below 35 kg.

Age and gender
No gender- or age-dependent effects in addition to the BW effect were observed.

Hepatic impairment
Two patients with mild hepatic impairment showed no differences in exposure. No dose adjustment for mild hepatic impairment is warranted. Moderate and severe hepatic impairment was not investigated. Therefore, the exposure and exposure-response relationship is unknown due to the unknown ASGPR expression status required for liver uptake.

Renal impairment
The predominant elimination pathway of the unconjugated full-length ASO (20-mer) and shortmers thereof is renal, and no data are available for patients with moderate to severe renal impairment.

6.2 Dose finding and dose recommendation

Dose finding was limited to 80 mg either 4 weekly or 8 weekly. Donidalorsen administered every 4 or 8 weeks produced statistically significant reductions in the HAE attack rate (number of investigator-confirmed HAE attacks per 4 weeks) compared to placebo in patients weighing ≥ 35 kg.
The reduction in dosing frequency from Q1M to Q2M for patients achieving a strong reduction in the HAE attack rate is deemed adequate based on the exposure-response relationship of donidalorsen.

6.3 Efficacy

The efficacy data are derived from one Phase 3 pivotal study (CS5), one Phase 2a study (CS2), one open label extension study (CS3), one OLE/Switch study (CS7) and two Phase 1 studies.
The main study (CS5) involved 91 patients from 12 years of age with hereditary angioedema who received donidalorsen (either every 4 weeks or every 8 weeks) or placebo. After 24 weeks, the average number of attacks per month was around 0.4 in patients given donidalorsen every 4 weeks and around 1 for those given donidalorsen every 8 weeks compared with around 2.3 for those given placebo. In addition, the study assessed the impact of treatment on patients' quality of life using a validated questionnaire measuring how the disease symptoms affect people's daily life.
Overall, the results of pivotal Study ISIS 721744-CS5 show that donidalorsen 80 mg administered subcutaneously every 4 weeks or every 8 weeks as a prophylactic treatment resulted in clinically

meaningful benefits on multiple measures of HAE disease activity, including QoL, and perceived control of disease compared with the placebo group. Additionally, in an exploratory analysis, donidalorsen treatment resulted in a nominally significant reduction in emergency room visits compared with placebo.
The efficacy and PK data and analyses presented in this report lead to the following conclusions:
The primary efficacy endpoint, comparison of the time-normalised number of investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25 between the donidalorsen-4 group and the placebo group, was met in this study. The least square mean (LSM) time-normalised investigator-confirmed HAE attack rate (per 4 weeks) from Week 1 to Week 25 was 0.44 for the donidalorsen-4 group and 2.26 for the placebo group, representing an 81% reduction relative to placebo for the donidalorsen-4 group (statistically significant $p < 0.001$).
Donidalorsen-4 subgroup analyses on the primary efficacy endpoint by age, sex, race, region, and predefined prophylactic therapy use, produced similar results compared with the overall donidalorsen-4 group. For adolescent patients (aged 12 to 17 years), a 97.1% decrease from Baseline (Run-in Period) in the time-normalised HAE attack rate (per 4 weeks) from Week 1 to Week 25 was observed.
All primary and secondary endpoint analyses assessing the donidalorsen-4 group were statistically or nominally significant compared with placebo. Of the 8 secondary endpoints in the hierarchical ranking strategy for the donidalorsen-8 group, all but 2 endpoints were statistically or nominally significant compared with placebo.
Data from supportive clinical trials confirm the efficacy profile from study CS5.

6.4 Safety

The safety data are derived from one Phase 3 pivotal study (CS5), one Phase 2a study (CS2), one open label extension study (CS3), one OLE/Switch study (CS7) and two Phase 1 studies.
The primary conclusions are derived from pivotal study CS5. Study CS2 is supportive for safety and is included in an integrated pool comprising placebo-controlled studies of CS5 and CS2 (Pool 1).
Additional supportive evidence for establishing the safety profile of donidalorsen was generated by pooling safety data from CS5, CS2, CS3, and CS7 (Pool 2).
The following AESIs were predefined: 1. Severe reductions in platelet counts < 50,000/mm^3 accompanied by an MB (major bleeding) event or CRNMB (clinically relevant non-major bleeding) event; or 2. Platelet count of < 25,000/mm^3 independently of an MB event or CRNMB event.
Additional safety analyses relevant to donidalorsen focused on organ systems of preferential distribution of ASO (hepatic and renal), and AEs known to be associated with subcutaneous ASO delivery (injection site events and flu-like reactions).
There was a high rate of TEAEs in pivotal study CS5 and study CS2. In CS5 the highest rate of AEs was in the placebo group (81.8%), followed by the donidalorsen-4 group (73.3%), and followed by the donidalorsen-8 group (60.9%), with a similar pattern seen in Pool 1. In Pool 2, with additional long-term exposure to donidalorsen (but no additional exposure to placebo), the proportion of patients who experienced TEAEs was 93.3% in the donidalorsen-4 group, 69.8% in the donidalorsen-8 group, and 82.1% in the placebo group.
In terms of TEAE severity, in CS5 the majority of TEAEs across all treatment groups were mild or moderate. A greater proportion of patients in the donidalorsen-8 group (8.7%) and the placebo group (9.1%) had severe TEAEs compared with the donidalorsen-4 group (2.2%). Of the 5 severe TEAEs, only 1 event was serious, and 4 TEAEs were unrelated to study drug. Only 3 severe events were in donidalorsen-treated subjects. In Pool 2 the majority of TEAEs were mild or moderate, and rates of severe TEAEs were similar across the donidalorsen and placebo arms, despite longer exposure in the donidalorsen arms. In the donidalorsen-4 group, 9.2% experienced severe TEAEs, including headache (2 patients), nausea (2 patients), and cardiac failure acute, toothache, constipation, pyrexia, COVID-19, gastroenteritis, pneumonia, mastoiditis, otitis media chronic, neck pain, torticollis, meningioma, pulmonary oedema, pruritus, and deep vein thrombosis (all in 1 patient each). In the donidalorsen-8 group, 7.0% had severe TEAEs, including epicondylitis, blood creatine phosphokinase increased, and spinal pain. In the 3 subjects that received donidalorsen-100 mg every 4 weeks, 33.3% (one patient) experienced a severe TEAE of dermatitis.

In terms of relatedness, in CS5 considerably more (42.2%) of the donidalorsen-4 group had related TEAEs compared with the donidalorsen-8 (17.4%) and placebo groups (27.3%). The majority of those AEs in donidalorsen groups were injection site reactions.
No SAE was reported in any patient treated with donidalorsen in CS5, or in Pool 1. In Pool 2, 12 SAEs were reported, and all bar one (spontaneous abortion) occurred while on donidalorsen-4. The SAEs were varied. In all but one case there is a clear indicator from the background history to suggest a non-causal relationship with donidalorsen. There has been one study death since the data cut-off date: death by suicide. The SAE that does appear to be related to donidalorsen is discussed in detail under Hypersensitivity reactions. This was a second hypersensitivity severe allergic anaphylactic type reaction which fulfilled Sampson's criteria.

6.5 Final clinical benefit risk assessment

The pivotal study ISIS 721744-CS5 met its primary endpoint, and the effect of the treatment is considered to be clinically relevant for patients with C1-INH HAE. The efficacy is also supported by the results from secondary endpoints and the second double-blind study (ISIS 721744-CS2). Moreover, the results from the longer-term open label trials support the maintenance of efficacy over time.
From a safety perspective, while effects on liver function (generally mild), and a reasonably high rate of ISRs have been observed in the donidalorsen-treated arms, the tolerability can be considered acceptable and manageable provided the issues raised are satisfactorily addressed, including further safety data from the two ongoing OLEs CS3 and CS7

The overall benefit /risk balance 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 Dawnzera 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.

Dawnzera 80 mg solution for injection in pre-filled pen

Composition

Active substances

Donidalorsen (a synthetically produced, chemically modified antisense oligonucleotide)

Excipients

Sodium dihydrogen phosphate (E 339), Disodium hydrogen phosphate (E 339), Sodium chloride, Water for injections. Hydrochloric acid (E 507) (for pH adjustment), Sodium hydroxide (E 524) (for pH adjustment).

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled pen (injection).
Each pre-filled pen contains 80 mg donidalorsen (equivalent to 84 mg donidalorsen sodium) in 0.8 mL of solution. Each mL contains 100 mg donidalorsen, equivalent to 105 mg donidalorsen sodium.
Clear, colourless to yellow solution (pH of approximately 7.4).

Indications/Uses

Dawnzera is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

Dosage/Administration

Treatment is to be initiated under the supervision of a physician experienced in the management of patients with HAE.

Posology
The recommended starting dose in adult and adolescent patients is 80 mg donidalorsen by subcutaneous injection. Doses should be administered once monthly.
A dosing interval of 80 mg once every 2 months may be considered if the patient is well controlled (e.g., attack free) for at least 3 months while receiving Dawnzera.

Missed dose

If a dose is missed, the patient or caregiver should be instructed to administer the dose as soon as possible. Thereafter, dosing should be resumed at the prescribed dosing frequency (once monthly or once every 2 months) from the date of the most recently administered dose.

Special dosage instructions

Elderly patients
No dose adjustment is required for patients above 65 years of age (see section “Pharmacokinetics”).

Patients with hepatic impairment
No dose adjustment of Dawnzera is required for patients with mild hepatic impairment (see section “Pharmacokinetics”). Dawnzera has not been studied in patients with moderate or severe hepatic impairment. Therefore, Dawnzera should not be used in patients with moderate or severe hepatic impairment.

Patients with renal impairment
No dose adjustment of Dawnzera is required for patients with mild renal impairment. Dawnzera has not been studied in patients with moderate or severe renal impairment or end stage renal disease. Therefore, Dawnzera should be used with caution in patients with moderate or severe renal impairment or end-stage renal disease.

Children and adolescents
The posology is the same in adults and adolescents aged 12 years and older. Dawnzera has not been studied in adolescent patients weighing less than 35 kg and should therefore not be used in these patients (see “Pharmacokinetics”).
The safety and efficacy of Dawnzera in children aged < 12 years have not been established. No data are available.

Changing from other HAE prophylactic medicinal products
The following treatment schedules (Table 1) are recommended for patients that are changing their HAE prophylactic therapy from berotralstat, a C1 esterase inhibitor, or lanadelumab to Dawnzera (see section “*Pharmacodynamics*”).

Table 1: Treatment schedule for patients changing from other prophylactic therapy to Dawnzera.

Other Prophylactic Therapy:	**Recommended treatment schedule when changing to Dawnzera:**
Berotralstat	Continue taking the current dose of berotralstat for 14 days after initiating treatment with Dawnzera.
C1 esterase inhibitor	Continue taking the current dose of C1 esterase inhibitor for 14 days after initiating treatment with Dawnzera.
Lanadelumab	Administer last dose of lanadelumab 14 days prior to initiating treatment with Dawnzera.

Method of administration

Dawnzera is only intended for subcutaneous use.

Dawnzera is to be administered as a subcutaneous injection in the abdomen, upper thigh region, or for caregivers only, the back of the upper arm. Rotation of the injection site is recommended.

Dawnzera must not be injected into areas where the skin is tender, bruised, red, hard, infected or discoloured.

After proper training on correct subcutaneous injection technique, a patient or caregiver may inject Dawnzera if their physician determines it is appropriate. Comprehensive instructions for administration using the pre-filled pen are provided in the package leaflet in the section instructions for use.

For further instructions on preparation and special precautions for handling, see section “Other information”.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.

Warnings and precautions

Hypersensitivity including anaphylaxis

Hypersensitivity reactions including anaphylaxis have been observed (see section “Undesirable effects”). In case of a severe hypersensitivity reaction, administration of Dawnzera must be stopped immediately and appropriate treatment must be initiated (see section “Contraindication”).

Patients must be advised on the signs and symptoms of hypersensitivity reactions and instructed to promptly seek medical attention and to discontinue use of Dawnzera if serious hypersensitivity reactions occur.

General

Dawnzera is not intended for treatment of acute HAE attacks. In case of a breakthrough HAE attack, individualised treatment should be initiated with an approved rescue medicinal product.

There are limited data available on the use of Dawnzera in HAE patients with HAE-nC1INH (see section “Pharmacodynamics”). It is recommended to perform genetic testing, if available, according to current HAE guidelines and to discontinue the treatment if clinical response is not observed.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Interactions

No clinical drug-drug interaction studies have been performed with donidalorsen.
In vitro studies show that donidalorsen is not a substrate or inhibitor of transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, BSEP), does not interact with medicinal products strongly bound to plasma proteins, and neither inhibits (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) nor induces (CYP1A2, CYP2B6, CYP3A4) cytochrome P450 (CYP) enzymes.
Donidalorsen is not expected to cause or be affected by drug-drug interactions mediated through drug transporters, plasma protein binding, or CYP enzymes.

Pregnancy, lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of donidalorsen in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section „Preclinical data“).

As a precautionary measure, it is preferable to avoid the use of Dawnzera during pregnancy.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of donidalorsen/metabolites in milk (see section „Preclinical data“).

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Dawnzera therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data on the effect of this medicinal product on human fertility are available. Donidalorsen had no effect on fertility and early embryonic development toxicity in murine models (see section „Preclinical data“).

Effects on ability to drive and use machines

Dawnzera has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) in patients treated with 80 mg donidalorsen every 4 weeks were injection site reactions (24.4%).
No deaths or serious adverse drug reactions occurred during clinical trials.

Tabulated list of adverse reactions

Adverse reactions associated with donidalorsen obtained from clinical studies are tabulated below. All ADRs are listed by system organ class and frequency; very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1 000, <1/100), rare (≥1/10'000, <1/1'000), very rare (<1/10'000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions to donidalorsen

System organ class	Adverse drug reaction	Frequency
Immune system disorders	Hypersensitivity (including anaphylaxis)	Common
General disorders and administration site conditions	Injection site reactions*	Very common (24.4%)

* Injection site reactions include also: discolouration, erythema, pain, pruritus, induration, haematoma, bruising, exfoliation, hypersensitivity and swelling.

Description of selected adverse reactions

Hypersensitivity including anaphylaxis

In clinical trials, a serious hypersensitivity reaction of anaphylaxis was reported in one patient. Symptoms included generalised rash, dyspnoea, chest pain and peri-oral swelling (see sections "Contraindications" and "Warnings and Precautions").

Injection site reactions

During double-blind, placebo-controlled trials, injection site reactions were observed. All injection site reactions were non serious, mild to moderate in severity, and resolved over time. In some patients, the injection site reactions such as injection site erythema, injection site pruritus, and injection site discolouration persisted for 2 or more days. In one patient who received higher than labelled doses in accordance with the protocol, injection site discoloration led to permanent discontinuation of treatment.

Paediatric population

The safety of Dawnzera has been established in adolescent patients aged 12 to 17 years in a double-blind placebo-controlled clinical trial that included a total of 7 adolescent patients supplemented by 4 Dawnzera naïve adolescent patients from an open label trial. The safety profile in these adolescents was similar to the profile observed in adults.

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 adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no available information to identify potential signs and symptoms of overdose. If symptoms should occur, symptomatic treatment is recommended. There is no antidote available.

Properties/Effects

ATC code

B06AC09
Pharmacotherapeutic group: Other haematological agents, drugs used in hereditary angioedema.

Mechanism of action

Donidalorsen is a 2'-O-methoxyethyl–modified antisense oligonucleotide (ASO) conjugated to a triantennary N-acetylgalactosamine ($GalNAc_3$) moiety that causes ribonuclease H1 (RNase H1) mediated degradation of prekallikrein (PKK) mRNA through selective binding to PKK mRNA, which results in reduced production of PKK protein. PKK is a pro-enzyme for plasma kallikrein, which results in the release of bradykinin, a potent vasodilator causing swelling and pain in HAE. In patients with HAE, C1 inhibitor (C1-INH) deficiency or dysfunction leads to excessive plasma kallikrein activity, bradykinin generation, and angioedema attacks. Donidalorsen lowers PKK concentration, preventing excessive bradykinin production in patients with HAE.

Pharmacodynamics

In Trial 1 in adult and paediatric patients (≥12 years) with HAE 1 or HAE 2 (see clinical efficacy below), a decrease in plasma PKK concentrations was observed at the first assessment (Week 4) following treatment with Dawnzera 80 mg. The mean percentage change from baseline to Week 24 in trough plasma PKK concentrations indicated reductions of 73% and 47% following treatment with Dawnzera 80 mg every 4 weeks and every 8 weeks, respectively, compared with a slight increase (2%) observed in the placebo group.

Clinical efficacy

The efficacy of Dawnzera for the prevention of angioedema attacks in patients with HAE due to C1-INH deficiency type 1 (HAE 1) or HAE due to C1-INH deficiency type 2 (HAE 2) was demonstrated in a 24-week multicenter, randomised, double blind, placebo-controlled trial (Trial 1) and a 16 week multicenter, randomised, double blind, placebo-controlled trial (Trial 3).

Trial 1- "OASIS-HAE", ISIS 721744-CS5

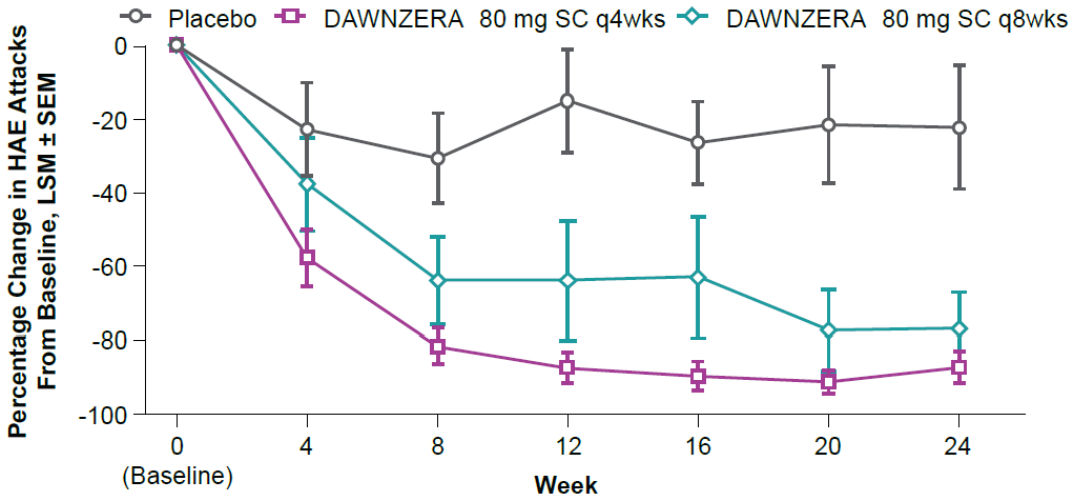
Trial 1 included 90 adult and paediatric patients (≥12 years) with at least 2 investigator-confirmed attacks during the 8-week run in period, who received at least 1 dose of study treatment. Patients

were randomised in a 2:1 ratio to 1 of 2 groups to receive study treatment either once every 4 weeks (q4wks group) or once every 8 weeks (q8wks group). Within each group, patients were randomised in a 3:1 ratio to receive Dawnzera 80 mg or a matching volume of placebo. The 2 placebo treated groups were combined for analysis. Patients were required to discontinue other prophylactic HAE medications prior to entering the trial; however, all patients were allowed to use rescue medications for treatment of any breakthrough HAE attacks.

Overall, 93% of patients had HAE 1. A history of laryngeal angioedema attacks was reported in 52% of patients, and 18% of patients were on prior prophylactic therapy. The median HAE attack rate during the prospective run-in period (baseline attack rate) was 2.85 attacks/4 weeks and an attack rate of >2 attacks/4 weeks was observed in 69% of patients overall.

Dawnzera administered every 4 or 8 weeks produced statistically significant reductions in the HAE attack rate (number of investigator-confirmed HAE attacks per 4 weeks) compared to placebo, meeting the primary endpoint in this trial. A sustained response to Dawnzera with mean decreases from baseline in the HAE attack rate was observed throughout the treatment period in the Dawnzera treatment groups as shown in Figure 1. All secondary endpoint analyses for the q4wks group and all but 2 secondary endpoint analyses for the q8wks group were statistically or nominally significant compared with placebo as shown in Table 3 and discussed further below.

Figure 1: Percentage change (LSM ± SEM) from baseline in the rate of investigator-confirmed HAE attacks/4 weeks in trial 1



HAE = hereditary angioedema; LSM = least square mean; q4wks = every 4 weeks; q8wks = every 8 weeks; SC = subcutaneous; SEM = standard error of the mean.

Table 3: Results of primary and secondary efficacy endpoints (full analysis set)

Endpoint Statistics	**Placebo (N=22)**	**Dawnzera 80 mg q4wks (N=45)**	**Dawnzera 80 mg q8wks (N=23)**
HAE attack rate per 4 weeks from baseline to Week 24*			
LS mean (95% CI) attack rate	2.26 (1.66, 3.09)	0.44 (0.27, 0.73)	1.02 (0.65, 1.59)

Endpoint Statistics	Placebo (N=22)	Dawnzera 80 mg q4wks (N=45)	Dawnzera 80 mg q8wks (N=23)
% Reduction (95% CI) relative to placebo		−81 (−89, −65)	−55 (−74, −22)
Wald chi-square p-value		<0.001†	0.004†
HAE attack rate per 4 weeks from Week 4 to Week 24			
LS mean (95% CI) attack rate starting from second dose (Week 4)	2.25 (1.59, 3.18)	0.30 (0.15, 0.58)	0.90 (0.53, 1.52)
% Reduction (95% CI) relative to placebo starting from second dose (Week 4)		−87 (−94, −72)	−60 (−79, −25)
Wald chi-square p-value		<0.001†	0.004†
Moderate or severe HAE attack rate per 4 weeks from Week 4 to Week 24			
LS mean (95% CI) moderate or severe attack rate starting from second dose (Week 4)	1.15 (0.72, 1.83)	0.12 (0.04, 0.35)	0.68 (0.37, 1.23)
% Reduction (95% CI) relative to placebo starting from second dose (Week 4)		−89 (−97, −66)	−41 (−72, 26)
Wald chi-square p-value		<0.001†	NS
HAE attacks per 4 weeks requiring acute therapy from Week 4 to Week 24			
LS mean (95% CI) HAE attacks requiring acute therapy starting from second dose (Week 4)	1.80 (1.23, 2.62)	0.15 (0.06, 0.39)	0.59 (0.31, 1.15)
% Reduction (95% CI) relative to placebo starting from second dose (Week 4)		−92 (−97, −77)	−67 (−85, −29)
Wald chi-square p-value		<0.001†	0.004‡

CI = confidence interval; HAE = hereditary angioedema; LS = least square; N = number of patients in the specific treatment group; NS = nonsignificant; q4wks = every 4 weeks; q8wks = every 8 weeks.
* Primary efficacy endpoint = comparison of the time normalised number of investigator-confirmed HAE attacks per 4 weeks from baseline to Week 24 between the Dawnzera 80 mg q4wks group and the placebo group.
† Reached statistical significance (p value <0.05).
‡ Reached nominal significance (p value <0.05).

Additional pre-defined study secondary endpoints included the proportion of responders to study drug and percentage of patients who had well controlled angioedema activity. The proportion of patients with a ≥50%, ≥70%, ≥90%, and 100% (attack free) reduction from baseline in HAE attack rate from Week 4 to Week 24 in the Dawnzera treatment group was 93%, 82%, 62%, and 53%, respectively, in the 80 mg q4wks group, and 83%, 65%, 48%, and 35%, respectively, in the 80 mg q8wks group, compared to 27%, 18%, 9%, and 9%, respectively, in the placebo group. The number of patients who had well controlled disease at Week 24 in the Dawnzera treatment group based on the Angioedema Control Test (AECT) score ≥10 at Week 24 was 41 (91%) (p-value <0.001) in the 80 mg q4wks group and 17 (74%) (p-value 0.028) in the 80 mg q8wks group, compared to 9 (41%) in the placebo group.

Health-related Quality of Life

An improvement was observed for Dawnzera treatment groups compared to placebo in the Angioedema Quality of Life Questionnaire (AE-QoL) total score. A reduction of 6 points is considered a clinically meaningful improvement. For the total AE-QoL score at Week 24, the least square mean change from baseline in the Dawnzera treatment group was −24.8 and −19.9 for the 80 mg q4wks group and 80 mg q8wks group, respectively, compared to −6.2 in the placebo group (p <0.001 and p=0.010, respectively).

Trial 2 – "OASISplus", ISIS 721744-CS7

A total of 147 adult and paediatric patients (≥12 years) with HAE 1 or HAE 2 received at least 1 dose of Dawnzera in an open label extension trial (Trial 2) of up to 3 years. Of these 147 patients, 83 patients were previously treated with Dawnzera or placebo in Trial 1 and were included in the open label extension rollover group of this study. The other 64 patients were previously maintained on other HAE prophylactic medications (berotralstat, C1 esterase inhibitors, or lanadelumab) for at least 12 weeks prior to the Trial 2 run in period and were included in the non-rollover group of this study as they were not previously enrolled in a Dawnzera study.

Open label Extension Rollover Group (Trial 1 Rollover Patients):

Rollover patients from Trial 1 continued in the same Dawnzera 80 mg q4wks or q8wks treatment groups in Trial 2; however, patients from the q8wks group that were not attack free for ≥8 weeks during Week 16 to 24 in Trial 1, received Dawnzera 80 mg every 4 weeks in Trial 2. Patients who received placebo in Trial 1 received Dawnzera 80 mg every 4 weeks in Trial 2. The mean HAE attack rate for all rollover patients was 0.22 attacks/4 weeks during Trial 2, showing a sustained mean reduction in HAE attack rate of 93% compared to the baseline attack rate of 3.42 attacks/4 weeks in Trial 1 after 76 weeks of treatment. On the basis of the AECT scores (score ≥10), 13/64 (20%) in the 80 mg q4wks group had well controlled disease in the Dawnzera treatment group at baseline and 42/46 (91%) at Week 24, and 5/12 (42%) at baseline and 9/9 (100%) in the 80 mg q8wks group at Week 24.

Health-related quality of life

The mean AE-QoL total score decreased from 46.3 (SD 16.6) (n=69) at baseline to 21.0 (SD 16.1) (n=47) at Week 25 in the q4wks group and from 41.8 (SD 18.4) (n=14) to 12.4 (SD 9.0) (n=9) in the q8wks group, corresponding to a mean change of -27.6 (95% CI -32.2, -23.1) and -23.9 (95% CI -37.9, -23.1), respectively.

Non-rollover Group (Patients Previously Maintained on Other HAE Long-Term Prophylactic Medications):

All non-rollover patients received Dawnzera 80 mg every 4 weeks in Trial 2 (n=64). Patients were to continue to take their other HAE prophylactic treatment during the run-in period as per the respective

recommended treatment schedules based on the half-life of the individual medicinal products (see section “Dosage/Administration”). The mean HAE attack rate for all non-rollover patients was 0.30 attacks/4 weeks from Week 0 to Week 52, showing a sustained mean reduction in HAE attack rate of 66% compared to the baseline attack rate of 0.85 attacks/4 weeks (for the subgroups the percent change included reductions of 51% for the prior lanadelumab group, 76% for the prior berotralstat group, and 78% for the prior C1-esterase inhibitor group). Overall, no increase in HAE attack rate was seen during the transition period from other HAE prophylactic medications to Dawnzera. Efficacy data up to week 52 and disease control available data (up to Week 16) measured by AECT score are reported in Table 4.

Health-related quality of life

Health-related quality of life available data (up to Week 16) measured by the AE-QoL score are reported in Table 4.

Table 4: Non-rollover group efficacy, AECT, and AE-QoL data.

	Lanadelumab n = 31	**Berotralstat n = 11**	**C1-esterase inhibitor n = 22**	**Switch patients Total n = 64**
Time normalised attack rate (per 4 weeks) from Week 0 to Week 52				
Baseline Mean (95% CI)	0.69 (0.29, 1.09) (n = 31)	1.80 (0.51, 3.09) (n = 11)	0.61 (0.19, 1.04) (n = 22)	0.85 (0.53, 1.17) (n = 64)
Week 0 – 52 Mean (95% CI)	0.27 (0.15, 0.39) (n = 31)	0.35 (0.13, 0.58) (n = 11)	0.33 (0.04, 0.62) (n = 22)	0.30 (0.19, 0.42) (n = 64)
% Change from baseline to week 0 to week 52 period Mean (95% CI)	-51.05 (-78.77, -23.32) (n = 15)	-76.47 (-93.38, -59.56) (n = 9)	-78.20 (-97.31, -59.09) (n = 11)	-66.12 (-79.69, -52.55) (n = 35)
Time normalised attack rate (per 4 weeks) from Week 4 to Week 52				
Baseline Mean (95% CI)	0.69 (0.29, 1.09) (n = 31)	1.80 (0.51, 3.09) (n = 11)	0.61 (0.19, 1.04) (n = 22)	0.85 (0.53, 1.17) (n = 64)
Week 4 – 52 Mean (95% CI)	0.28 (0.16, 0.41) (n = 30)	0.21 (0.05, 0.38) (n = 11)	0.29 (0.00, 0.59) (n = 22)	0.27 (0.16, 0.39) (n = 63)
% Change from baseline to week 4 to week 52 period Mean (95% CI)	-52.82 (-79.89, -25.74) (n = 15)	-87.04 (-100.33, -73.76) (n = 9)	-78.30 (-97.24, -59.37) (n = 11)	-69.63 (-83.01, -56.25) (n = 35)
Time normalised moderate or severe attack rate (per 4 weeks) from Week 4 to Week 52				
Baseline Mean (95% CI)	0.51 (0.16, 0.85) (n = 31)	0.94 (0.12, 1.76) (n = 11)	0.38 (0.01, 0.74) (n = 22)	0.54 (0.30, 0.78) (n = 64)
Week 4 – 52 Mean (95% CI)	0.20 (0.10, 0.30) (n = 30)	0.09 (0, 0.19) (n = 11)	0.16 (-0.06, 0.37) (n = 22)	0.17 (0.08, 0.25) (n = 63)
% Change from baseline to week 4 to week 52 period Mean (95% CI)	-65.55 (-92.24, -38.85) (n = 11)	-98.25 (-101.11, -95.38) (n = 7)	-95.09 (-108.72, -81.45) (n = 5)	-81.92 (-95.60, -68.24) (n = 23)
Time normalised attack rate (per 4 weeks) requiring HAE acute therapy from Week 4 to Week 52				
Baseline Mean (95% CI)	0.46 (0.12, 0.80) (n = 31)	1.66 (0.30, 3.01) (n = 11)	0.55 (0.13, 0.97) (N = 22)	0.69 (0.38, 1.01) (n = 64)
Week 4 – 52 Mean (95% CI)	0.24 (0.13, 0.36) (n = 30)	0.18 (0.01, 0.34) (n = 11)	0.29 (-0.01, 0.58) (n = 22)	0.25 (0.13, 0.36) (n = 63)

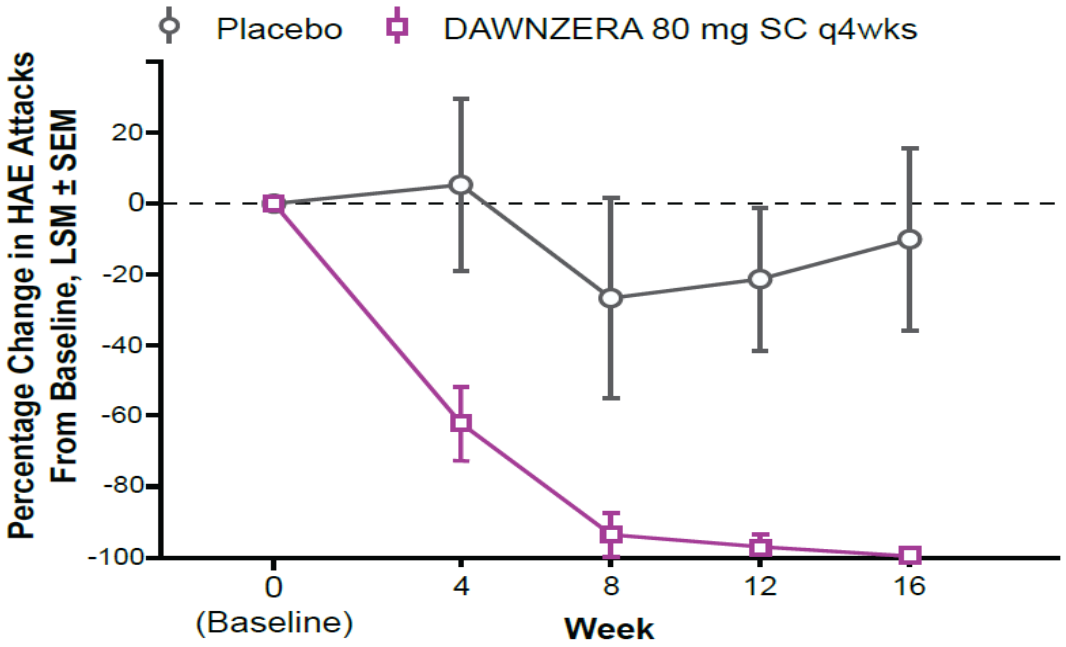
	Lanadelumab n = 31	Berotralstat n = 11	C1-esterase inhibitor n = 22	Switch patients Total n = 64
% Change from baseline to week 4 to week 52 period Mean (95% CI)	-44.95 (-79.56, -10.33) (n = 10)	-91.56 (-99.39, -83.72) (n = 7)	-77.25 (-98.00, -56.49) (n = 10)	-68.99 (-84.33, -53.65) (n = 27)
AECT score from Week 0 to Week 16				
Baseline Mean (95% CI)	12.0 (10.8, 13.2) (n = 31)	8.7 (5.3, 12.1) (n = 11)	11.7 (10.2, 13.3) (n = 22)	11.3 (10.4, 12.3) (n = 64)
Week 16 Mean (95% CI)	13.9 (13.0, 14.8) (n = 27)	13.4 (11.7, 15.1) (n = 10)	14.2 (13.3, 15.1) (n = 20)	13.9 (13.4, 14.5) (n = 57)
% Change from baseline to week 17 Mean (95% CI)	25.98 (10.63, 41.33) (n = 27)	65.71 (11.20, 120.23) (n = 9)	33.93 (10.92, 56.95) (n = 20)	35.21 (21.89, 48.53) (n = 56)
AE-QoL total score from Week 0 to Week 16				
Baseline Mean (95% CI)	33.58 (25.85, 41.31) (n = 30)	37.17 (22.13, 52.20) (n = 11)	29.76 (21.62, 37.91) (n = 21)	32.92 (27.86, 37.99) (n = 62)
Week 16 Mean (95% CI)	24.53 (17.11, 31.95) (n = 25)	19.56 (10.12, 28.99) (n = 10)	21.71 (16.01, 27.41) (n = 17)	22.65 (18.47, 26.83) (n = 52)
% Change from baseline to week 16 Mean (95% CI)	-20.08 (-56.99, 16.84) (n = 25)	-29.07 (-65.07, 6.93) (n = 10)	-23.95 (-42.09, -5.80) (n = 17)	-23.07 (-41.89, -4.16) (n = 52)

Trial 3 – Phase 2 Trial, ISIS 721744-CS2

Trial 3 included 20 adult patients (≥18 years) with at least 2 investigator-confirmed attacks during the 8-week run-in period, who received at least 1 dose of study treatment. Patients were randomised in a 2:1 ratio to Dawnzera 80 mg once every 4 weeks or placebo once every 4 weeks. Patients were required to discontinue other prophylactic HAE medications prior to entering the trial; however, all patients were allowed to use rescue medications for treatment of any breakthrough HAE attacks. Overall, 90% of patients had HAE 1. A history of laryngeal angioedema attacks was reported in 60% of patients and no patients were on prior prophylactic therapy. The mean attack rate during the prospective run-in period (baseline attack rate) was 2.7 attacks/4 weeks and an attack rate of ≥2 attacks/4 weeks were observed in 65% of patients overall.

Dawnzera produced a clinically significant reduction in the HAE attack rate (number of investigator-confirmed HAE attacks per 4 weeks) compared to placebo, meeting the primary endpoint in this trial, as shown in Figure 2 and Table 5.

Figure 2: Percentage change (LSM ± SEM) from baseline in the rate of investigator-confirmed HAE attacks/4 weeks in Trial 3



HAE = hereditary angioedema; LSM = least square mean; q4wks = every 4 weeks; SC = subcutaneous; SEM = standard error of the mean.

Table 5: Results of primary and secondary efficacy endpoints (ITT population)

Endpoint Statistics	Placebo (N=6)	Dawnzera 80 mg q4wks (N=14)
HAE Attack Rate per 4 Weeks from Baseline to Week 16*		
LS mean (95% CI) attack rate	2.29 (1.54, 3.41)	0.22 (0.10, 0.50)
% Reduction (95% CI) relative to placebo		−90 (−96, −76)
Wald chi-square p-value		<0.001
HAE Attack Rate per 4 Weeks from Week 4 to Week 16		
LS mean (95% CI) attack rate starting from second dose (Week 4)	2.13 (1.13, 4.01)	0.06 (0.01, 0.61)
% Reduction (95% CI) relative to placebo starting from second dose (Week 4)		−97 (−100, −69)
Wald chi-square p-value		0.003

CI = confidence interval; HAE = hereditary angioedema; ITT = Intent-to-Treat; LS = least square; N = number of patients in the specific treatment group; q4wks = every 4 weeks.
* Primary efficacy endpoint = comparison of the time-normalised number of investigator-confirmed HAE attacks per 4 weeks from baseline to Week 16 between the Dawnzera 80 mg q4wks group and the placebo group.

The least square mean moderate or severe HAE attack rate from Week 4 to Week 16 in the Dawnzera treatment group was 0.05, compared to 1.20 in the placebo group, showing a percentage reduction of 96%. The proportion of patients with a ≥50%, ≥70%, ≥90%, and 100% (attack free) reduction from baseline in HAE attack rate from Week 4 to Week 16 in the Dawnzera treatment group was 100%, 92%, 92%, and 92%, respectively, compared to 33%, 17%, 0%, and 0%, respectively, in the placebo group. The least square mean number of investigator-confirmed HAE attacks per 4

weeks requiring acute therapy from Week 4 to Week 16 was 0.06 in the Dawnzera treatment group and 1.16 in the placebo group; showing a percentage reduction of 95%.

Health related quality of life

An improvement was observed for the Dawnzera treatment group compared to the placebo group in the AE-QoL total score. For the total AE-QoL score at Week 16, the least square mean change from baseline in the Dawnzera treatment group was −26.9 compared to −6.2 with placebo.

Open label arm for patients with HAE with normal C1INH (HAE-nC1INH)

Trial 3 also included an open label arm for patients with HAE-nC1INH which included 3 adult patients who received Dawnzera 80 mg every 4 weeks. A reduction in mean HAE attack rate from 4.23 attacks/4 weeks during the run-in period to 1.52 attacks/4 weeks from baseline to Week 16 was observed in this group.

Trial 4 – Phase 2 Open-Label Extension Trial, ISIS 721744-CS3

Patients who completed Trial 3 were eligible to rollover into Trial 4, an open label extension trial of up to 4 years. A total of 17 adult patients with HAE 1 or HAE 2 received at least 1 dose of Dawnzera in Trial 4. The mean HAE attack rate for these patients was 0.06 attacks/4 weeks during Trial 4, showing a sustained mean reduction in HAE attack rate of 96% compared to the baseline attack rate of 2.70 attacks/4 weeks in Trial 3.

Cardiac electrophysiology

No clinically significant prolongation of QTc interval was observed at the recommended dosage of Dawnzera 80 mg every 4 weeks or every 8 weeks.

Immunogenicity

The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADAs in the studies described below with the incidence of ADAs in other studies, including those of donidalorsen or of other ASO products.

In Trial 1, with a treatment duration up to 24 weeks, the incidence rate of treatment emergent ADAs in adult and paediatric patients (≥12 years) with HAE was 20% (9 of 45 patients) in the Dawnzera 80 mg q4wks group and 22% (5 of 23 patients) in the Dawnzera 80 mg q8wks group. In Trial 2, an open label extension trial, patients that rolled over from Trial 1 continued treatment with Dawnzera in the 80 mg q4wks or q8wks groups for up to 3 years (current median exposure duration of 227 days) and showed an incidence rate of treatment emergent ADAs of 36% (25 of 69 patients) in the Dawnzera 80 mg q4wks group and 21% (3 of 14 patients) in the Dawnzera 80 mg q8wks group. The incidence rate of treatment emergent ADAs was 42% (27 of 64 patients) for the non-rollover, Dawnzera naïve patients who were previously treated with berotralstat, C1 esterase inhibitors, or lanadelumab before

receiving Dawnzera 80 mg every 4 weeks for a current median exposure duration of 253 days in Trial 2.
The presence of ADAs did not affect donidalorsen plasma C_{max}, but increased C_{trough} was observed. The development of ADAs was not found to affect the pharmacodynamics, safety, or efficacy of Dawnzera in these patients.

Elderly patients
The safety and effectiveness of Dawnzera for prophylaxis to prevent attacks of HAE were evaluated in a subgroup of patients 65 years and older. Use of Dawnzera in this population is supported by evidence from Trials 1 and 3 that included 3 geriatric patients (≥65 years) supplemented by 2 Dawnzera naïve geriatric patients from an open label trial (Trial 2) that were previously maintained on other HAE prophylactic therapies and not previously enrolled in Trial 1. The safety profile and reduction in HAE attack rate in these geriatric patients were similar to those observed in younger adult patients.

Paediatric population
The safety and effectiveness of Dawnzera for prevention of attacks of HAE have been studied in paediatric patients 12 years and older. Use of Dawnzera in this population is supported by evidence from Trial 1 that included adults and a total of 7 adolescent patients (12 to 17 years) supplemented by 4 Dawnzera naïve adolescent patients from an open label trial (Trial 2) that were previously maintained on other HAE prophylactic therapies and not previously enrolled in Trial 1. The safety profile and reduction in HAE attack rate in these adolescents were similar to those observed in adults (see section “Undesirable effects”).
The safety and effectiveness of Dawnzera in paediatric patients less than 12 years of age have not been established.

Pharmacokinetics

The pharmacokinetic properties of donidalorsen were evaluated following subcutaneous administration of multiple doses every 4 weeks in healthy subjects and every 4 weeks or every 8 weeks in patients with HAE.
Population estimates (Geometric Mean) of steady state maximum plasma concentration ($C_{max,ss}$), trough plasma concentration ($C_{trough,ss}$), and area under the plasma concentration time curve over the dosing interval ($AUC_{\tau,ss}$) are presented in Table 6. No accumulation of donidalorsen C_{max} and AUC was observed in plasma after repeated dosing every 4 weeks.

Table 6: Summary of Simulated Pharmacokinetic Parameters from Population Pharmacokinetic Analysis Following Dosing of Dawnzera 80 mg q4wks or 80 mg q8wks in Patients with HAE at Steady State.

Pharmacokinetic Parameters (Geometric Mean)	Dawnzera	
	80 mg q4wks	80 mg q8wks
$C_{max,ss}$ (ng/mL)	417	416
$C_{trough,ss}$ (ng/mL)	0.755	0.255
$AUC_{\tau,ss}$ (ng·h/mL)	5240	5210

$AUC_{\tau,ss}$ = area under the plasma concentration time curve over the dosing interval at steady state; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{trough,ss}$ = trough plasma concentration at steady state; q4wks = every 4 weeks; q8wks = every 8 weeks.

Pharmacokinetics

Absorption

Following subcutaneous administration, donidalorsen is absorbed with the time to maximum plasma concentration of approximately 2.5 hours post dose, based on population estimates.

Distribution

Donidalorsen is expected to distribute primarily to the liver and kidney cortex after subcutaneous dosing. The population estimate of apparent volume of distribution for the central (Vc/F) and peripheral (Vp/F) compartment were 69.8 L and 1840 L, respectively. Donidalorsen is highly bound to human plasma proteins (>98% bound) *in vitro*.

Metabolism

Donidalorsen is metabolised by endo- and exonucleases to short oligonucleotide fragments of varying sizes within the liver. The GalNAc moiety of donidalorsen is cleaved from the ASO portion by rapid hydrolysis once distributed to tissues.

Elimination

The population estimate of the terminal elimination half-life of the ASO moiety of donidalorsen in a typical patient with HAE is approximately 1 month. The mean fraction of unchanged ASO eliminated in urine was less than 1% of the administered dose in healthy subjects within 24 hours. Linker related metabolites are minimally released to circulation and subsequently rapidly excreted to urine or faeces.

Kinetics in specific patient groups

Population analyses showed no clinically meaningful differences in the pharmacokinetics of donidalorsen based on sex (79 Male, 98 Female), ethnicity (Black or African American, Caucasian), geographical region, disease status.

Liver impairment

Population analyses showed no clinically meaningful differences in the pharmacokinetics of donidalorsen in patient with normal liver function (N=175) or mild hepatic impairment (total bilirubin ≤ 1 × ULN and AST > 1 × ULN, or total bilirubin > 1 to 1.5 × ULN and any AST [N=2]). Donidalorsen has not been studied in patients with moderate or severe hepatic impairment.

Renal impairment

Population based analyses showed no clinically meaningful differences in the pharmacokinetics of donidalorsen in patients with normal renal function (N=161) or mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m^2[N=16]). Donidalorsen has not been studied in patients with moderate or severe renal impairment, or end stage renal disease.

Children and adolescents

Population analyses showed no clinically meaningful differences in the pharmacokinetics of donidalorsen based on age (12 to <18 years [N=6]; 18 to <65 years [N=169]; ≥65 years [N=2]). Population-based analyses showed differences in the pharmacokinetics of donidalorsen depending on body weight. The expected C_{max} is 1.4 times higher in a patient weighing 60 kg (10th percentile) and 0.46 times lower in a patient weighing 100 kg (90th percentile) compared to a patient weighing 70 kg (50th percentile). In the weight range studied, from 37 to 151.9 kg body weight, the differences are clinically not relevant. Donidalorsen has not been studied in children aged < 12 years and weighing less than 35 kg.

Preclinical data

Carcinogenesis

In a 6 month carcinogenicity study in transgenic (Tg.rasH2) mice, subcutaneous administration of donidalorsen (5, 10, 20, or 60 mg/kg) or a rodent specific surrogate (10 mg/kg) once every 2 weeks did not result in an increase in malignant tumors. No malignant tumors were found in a 2-year study in rats. This suggests lack of human carcinogenic risk.

Mutagenesis

Donidalorsen was negative for genotoxicity in *in vitro* (bacterial reverse mutation, chromosomal aberration in Chinese hamster lung cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Pregnancy, lactation and fertility

Subcutaneous administration of donidalorsen (0, 5, 10, or 20 mg/kg/week) or a rodent active inhibitor of PKK (5 mg/kg/week) to mice every other day throughout pregnancy and weekly throughout lactation produced no adverse effects on pre- and postnatal development.

In the mouse pre- and postnatal development study, the concentrations of donidalorsen in breast milk from lactating mice increased in a dose dependent manner at doses ≥10 mg/kg/week, but these concentrations of donidalorsen in breast milk were >3000 fold lower than the observed tissue concentrations. Even though donidalorsen was detected in the maternal mouse milk, systemic exposure in pups was not expected due to the lack of oral absorption of donidalorsen.

In animal studies, administration of donidalorsen or a pharmacologically active rodent specific surrogate in a combined fertility and embryofetal development toxicity study in mice did not result in effects on male and female fertility or embryofetal development.
Subcutaneous administration of donidalorsen (0, 1, 4, or 10 mg/kg/week) or a rodent active inhibitor of prekallikrein (PKK) (4 mg/kg/week) to male and female mice weekly, prior to and during mating, and continuing every other day in females throughout the period of organogenesis, resulted in no adverse effects on fertility, pregnancy, or embryofetal development.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date marked as “EXP” on the pack.
Dawnzera may be stored in the original carton below 30°C for a single period of up to 6 weeks, but not beyond the expiry date. In this case, the disposal date must be entered in the designated area on the original packaging.

Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not freeze. Do not expose to heat.
Keep out of the reach of children.

Instructions for handling

Prior to initiation, patients and/or caregivers must be trained on proper preparation and administration of Dawnzera (see Instructions for Use in the Patient Information).

- The single-dose pre-filled pen should be removed from the refrigerator 30 minutes prior to the injection to reach room temperature. Other warming methods must not be used.
- The pre-filled pen must be inspected visually before use. The solution should appear clear and colourless to yellow. The pre-filled pen must not be used if cloudiness, particulate matter, or discolouration is observed prior to administration.
- Dawnzera is to be administered as a subcutaneous injection in the abdomen, upper thigh region, or for caregivers only, the back of the upper arm.
- Dawnzera must not be injected into areas where the skin is tender, bruised, red, or hard.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

69883 (Swissmedic)

Packs

Pack size of one pre-filled pen. [B]

Marketing authorisation holder

Otsuka Pharmaceutical (Switzerland) GmbH, 8152 Opfikon

Date of revision of the text

June 2026