# EU Risk Management Plan for: Donidalorsen

**RMP version to be assessed as part of this application:**

RMP Version number: 1.1

Data Lock Point for this RMP: 27 Jan 2025

Date of Final Sign Off: 10 Nov 2025

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission.

Summary of significant changes in this RMP:

| RMP Part / Module / Annex | Significant Changes |
|---|---|
| Part II /Module SI: Epidemiology of the Indication(s) and target population (s) | Not Applicable |
| Part II /Module SII - Non-clinical part of the safety specification | Not Applicable |
| Part II /Module SIII - Clinical trial exposure | Not Applicable |
| Part II /Module SIV - Populations not studied in clinical trials | SIV.1: Hepatic impairment changed from "Yes" to "No".<br>Pregnancy/lactation updated to 2 separate terms: "Use in Pregnancy" and "Use during Breastfeeding". |
| Part II /Module SV - Postauthorisation experience | Not Applicable |
| Part II /Module SVI - Additional EU requirements for the safety specification | Not Applicable |
| Part II /Module SVII - Identified and potential risks | The module was updated as requested in "CHMP day 180 list of outstanding issues" document<br>**Additional updates made as per "Responses to Day 203 List of Outstanding Issues – Clinical and Risk Management Plan" List of Outstanding Issues – Clinical and Risk Management Plan"* |

| RMP Part / Module / Annex | Significant Changes |
|---|---|
| Part II /Module SVIII - Summary of the safety concerns | The module was updated as requested in "CHMP day 180 list of outstanding issues" document<br>**Additional updates made as per request on Day 203 updated Rapporteur's Joint assessment reports of D195 "List of Outstanding Issues – Clinical and Risk Management Plan" List of Outstanding Issues – Clinical and Risk Management Plan"* |
| Part III: Pharmacovigilance Plan (including postauthorisation safety studies) | Updates were made to address the request from "CHMP day 180 list of outstanding issues" document |
| Part IV: Plans for postauthorisation efficacy studies | *Not Applicable* |
| Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) | Updates were made to address the request from "CHMP day 180 list of outstanding issues" document<br>**Additional updates made as per request on Day 203 updated Rapporteur's Joint assessment reports of D195 "List of Outstanding Issues – Clinical and Risk Management Plan" List of Outstanding Issues – Clinical and Risk Management Plan"* |
| Part VI: Summary of the risk management plan | Updates were made to address the request from "CHMP day 180 list of outstanding issues" document<br>**Additional updates made as per request on Day 203 updated Rapporteur's Joint assessment reports of D195 "List of Outstanding Issues – Clinical and Risk Management Plan" List of Outstanding Issues – Clinical and Risk Management Plan"* |
| Part VII: Annexes | Annex 2: Update to "safety concerns addressed"<br>Annex 3: Editorial alignment of the annex with the EMA Guidance on the format of the RMP<br>Annex 7: updated based on the updates in the RMP body. |

There are no previously submitted versions of this EU RMP that are still under evaluation by the Agency.

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**QPPV oversight declaration:** The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

# Table of Contents

# List of In-text Tables

# List of Abbreviations, Acronyms, and Definition of Terms

| Abbreviation/Acronym | Definition |
|---|---|
| ADA | Anti-drug antibody |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AE-QoL | Angioedema Quality of Life Questionnaire |
| ALT | Alanine Aminotransferase |
| aPTT | Activated Partial Thromboplastin Time |
| AST | Aspartate Aminotransferase |
| ASO | Antisense Oligonucleotide |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area Under the Curve |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| Cmax | Concentration Maximum |
| CNS | Central Nervous System |
| CS1 | ISIS 721744-CS1 |
| CS2 | ISIS 721744-CS2 |
| CS3 | ISIS 721744-CS3 |
| CS5 | ISIS 721744-CS5 |
| CS7 | ISIS 721744-CS7 |
| CS9 | ISIS 721744-CS9 |
| DLP | Data Lock Point |
| EEA | European Economic Area |
| EFD | Embryo-Fetal Development |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| eGFR | Estimated Glomerular Filtration Rate |
| EU | European Union |
| FDA | Food and Drug Administration |
| FEED | Fetal Early Embryonic Development |
| HADS | Hospital Anxiety and Depression Scale |
| HAE | Hereditary Angioedema |
| hERG | Human ether-a-go-go-related gene |
| IB | Investigator Brochure |
| ICH | The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| INN | International Non-proprietary Name |
| LICA | Ligand-Conjugated Antisense |
| MAA | Marketing Authorization Application |
| MOE | Methoxyethyl |
| mRNA | Messenger Ribonucleic Acid |
| N/A | Not Applicable |
| NOAEL | No Adverse Effects Level |
| PF4 | Platelet Factor 4 |
| PKK | Prekallikrein |
| PL | Package Leaflet |
| PLT | Platelets |
| PPND | Pre- and Post- Natal Development |
| PRAC | Pharmacovigilance Risk Assessment Committee |

| Abbreviation/Acronym | Definition |
|---|---|
| PRO | Patient Reported Outcomes |
| PSUR | Periodic Safety Update Report |
| PT | Preferred Term |
| Q4W | Every 4 weeks |
| Q8W | Every 8 weeks |
| QPPV | Qualified Person Responsible for Pharmacovigilance |
| RMP | Risk Management Plan |
| SOC | System Organ Class |
| SLE | Systemic Lupus Erythematosus |
| SmPC | Summary of Product Characteristics |
| SC | Subcutaneous |
| sNDA | Supplement New Drug Application |
| TEAE | Treatment Emergent Adverse Event |
| ULN | Upper Limit of Normal |
| US | United States |
| WPAI | Work Productivity and Activity Impairment questionnaire |

# 1 PART I: PRODUCT(S) OVERVIEW

| Table 1-1 Active Substance Information | |
|---|---|
| **Active substance(s) (INN or common name)** | Donidalorsen |
| **Pharmacotherapeutic group(s) (ATC code):** | Other haematological agents, drugs used in hereditary angioedema,<br>ATC code: not yet assigned |
| **Name of marketing authorisation applicant** | Otsuka Pharmaceutical Netherlands B.V.<br>Herikerbergweg 292<br>1101 CT Amsterdam<br>Netherlands |
| **Medicinal products to which this RMP refers:** | donidalorsen |
| **Invented name of the product in the European Economic Area (EEA)** | Dawnzera |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product** | Chemical class: Antisense Oligonucleotide (ASO) |
| | Summary of mode of action:<br>Donidalorsen is an antisense oligonucleotide GalNAc conjugate that causes hepatic targeted degradation of Prekallikrein (PKK) mRNA through direct binding to the PKK mRNA, which results in a reduction of plasma PKK protein. |
| | Important information about its composition:<br>none |
| **Hyperlink to the Product Information** | Product Information – Module 1.3.1 |
| **Indication(s) in the EEA** | Dawnzera is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. |
| | Proposed (if applicable):<br>Not applicable |
| **Dosage in the EEA** | The recommended dose is 80 mg donidalorsen by subcutaneous injection in adults and children >12 years. Doses should be administered once monthly. |
| | Proposed (if applicable):<br>Not applicable |
| **Pharmaceutical form(s) and strengths** | Each pre-filled pen contains 80 mg donidalorsen, equivalent to 84 mg donidalorsen sodium salt in 0.8mL of solution.<br>Sterile, preservative-free solution for subcutaneous injection<br>Clear, colourless to slightly yellow solution (target pH 7.4) |
| | Proposed (if applicable): Not applicable |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |

# 2 PART II: Module SI- SAFETY SPECIFICATION

## 2.1 Module SI: Epidemiology of the Indication and Target Population(s)

Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by deficiency of C1 inhibitor (HAE-C1-INH); the C1 inhibitor may be truly deficient due to genetic mutations (HAE-C1INH-Type 1) or dysfunctional (HAE-C1-INH-Type 2). More than 150 mutations have been identified.[1] Type I comprises 85% and Type 2 comprises 15% of cases of HAE.[2] A deficiency of functional C1 inhibitor leads, through a cascade of factors, to an excess of bradykinin, which promotes vascular permeability and results in recurrent episodes of angioedema in the skin or upper gastrointestinal and respiratory tracts. In a third, uncommon form of HAE the syndrome manifests itself despite normal C1 inhibitor levels (HAE-nC1-INH); this form occurs primarily in women.[3] The initial screening test for HAE is measurement of C4 levels in serum, which are decreased in HAE; a positive finding is then confirmed by measurement of the C1 inhibitor protein levels and activity.[4,5]

**Incidence**

There are no data available regarding the incidence rate of HAE.

**Prevalence**

Estimates of HAE prevalence range from 1 in 150,000 to 1 in 10,000[6] but most studies report prevalence as 1 in 50,000-67,000.[7,8] Roche *et al*. (2005) assessed the prevalence of HAE in Spain in July 1999[9] and reported 1.09 cases per 100,000 population; the mean age of onset of symptoms was 12.6 years and mean age of diagnosis was 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.[10]

**Demographics of the population in the proposed indication and risk factors for the disease**

***Age of Onset***

Hereditary angioedema typically first appears during childhood or adolescence and then persists throughout life.[11] 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.[12]

### *Gender and Race/Ethnicity*

Population-based studies have found no predominance of HAE by gender[7,9,12] although experts have suggested that the disease may be more severe in women.[2] The HAE-nC1-INH is more common in women than in men but is so rare that it does not impact the overall gender balance of HAE.[13] No differences by ethnic group have been reported.[2,11]

### *Risk Factors*

The primary risk factor for HAE is genetic.[14] Donaldson *et al*. reported that most HAE results from a genetic deficiency in C1 inhibitor levels.[15] Subsequent studies have shown that mutations within one of the two alleles of the SERPING1 gene lead to deficient C1 inhibitor levels and an autosomal dominant pattern of inheritance.[16] The SERPING1 gene is heterogeneous within the general population, and a variety of mutations can lead to type 1 HAE.[17] Multiple family pedigrees with HAE have been described as having SERPING1 heterozygosity and an autosomal dominant pattern of inheritance.[18] A few case reports describe homozygous mutations.[19] It is estimated that in 25% of cases the mutation arises as a spontaneous mutation.[20]

## Main treatment options

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, as specific treatments were not available, antihistamines, corticosteroids and epinephrine were utilized for acute attacks, despite a lack of evidence that they were effective.[21] Since 2008, various forms of C1 inhibitors have become available. Two randomized placebo-controlled trials demonstrated the efficacy of Cinryze, a human plasma-derived C1 inhibitor concentrate which is approved in Europe.[22,23] Another agent, ecallantide, is FDA-approved and available in the US for acute attacks.

Short-term prophylaxis (STP) in HAE involves preventive treatment before specific events that may trigger attacks, like medical, surgery or dental procedures. It aims to minimize or prevent HAE attacks during or following these triggers. The WAO/EAACI guidelines recommend the use of intravenous plasma-derived C1 inhibitor as first line STP. Fresh frozen plasma (FFP) may be used for short-term prophylaxis, but it is not as safe as intravenous pdC1-INH concentrate and is a second-line agent because of the greater risk of blood borne disease transmission and allosensitization. Attenuated androgens (e.g., danazol) have been recommended in the past for pre-procedural

prophylaxis as an alternative to intravenous pdC1-INH concentrates, but intravenous pdC1-INH concentrate is considered the prophylactic agent of choice.[24]

For long-term prophylaxis, androgens have been utilized 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.[25,26] Antifibrinolytics, such as tranexamic acid, have also been utilized for this purpose but careful studies have not clearly demonstrated efficacy. Lanadelumab, garadacimab and berotralstat, and kallikrein inhibitors, are available for use as prophylactic agents. Multiple other agents are currently in various stages of clinical development.[27]

### Natural history of HAE in the untreated population, including mortality and morbidity

Most episodes of angioedema among those with HAE are self-limited, but attacks can last for several days, be painful, and lead to disfigurement and absence from work. The frequency of angioedema attacks is variable. Before availability of long term prophylaxis, one-third of HAE patients had more than one attack per month, while 40% had 6-11 attacks per year, and 30% had infrequent attacks.[20] More recently, Mendivil et al., reported a mean (SD) of 12.5 (14.1) attacks in the past 6 months with the most recent attack reported within the past month in 79.7% of patients.[28] Unpredictability of HAE attacks causes substantial anxiety and negatively impacts personal and professional life; self-reported rates of depression, fatigue, fear, shame, and loss of productivity are all worse among HAE patients than in the background population.[29] Up to 3% of all attacks can involve the larynx, and laryngeal edema can lead to death from asphyxiation.[30] An international 2021 systematic review of the mortality associated with HAE included 23 articles and 3,292 patients and identified 411 deaths due to HAE since 1977.[31]

### Important comorbidities

Moderate to severe anxiety and depression were reported in 38.0% and 17.4% of HAE patients, respectively, as measured using the Hospital Anxiety and Depression Scale (HADS). The severity of anxiety and depression was associated with poorer quality of life and productivity, measured using the AECT (mean overall score 8.00 [moderate perceived disease control]), AE-QoL (Angioedema Quality of Life Questionnaire), WPAI, and SF-12v2 (Short Form 12 item version 2). Scores for AECT, AE-QoL, and WPAI were also worse with a higher number of attacks.[28]

Besides the above referenced psychiatric implications, 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.[32,33,34] In one study of 157 patients with HAE, 19 (12%) had an autoimmune disorder[35] such as inflammatory bowel disease, Sjogren's syndrome, lupus, or glomerulonephritis.

## 2.2 Part II: Module SII -Non-clinical Part of the Safety Specification

The nonclinical toxicology program for donidalorsen includes repeat-dose studies in CD-1 mice and cynomolgus monkeys of up to 26- and 39-week duration, respectively. Plasma and/or tissue pharmacokinetics were assessed as part of the toxicity evaluation. The genetic toxicity of donidalorsen has been investigated in a battery of in vitro and in vivo assays, and its tumorigenic potential has been evaluated in a 27-week carcinogenicity study in Tg.rasH2 mice, and a 2-yr carcinogenicity study in Sprague Dawley (SD) rats which is ongoing. A range of reproductive and developmental toxicity studies have been performed in the mouse following SC administration, including combined fetal early embryonic development (FEED)/ embryo-fetal development (EFD) and pre- and postnatal development (PPND) studies in mice. An embryo-fetal development study (EFD) in rabbits was not conducted for donidalorsen based on the comprehensive coverage provided by the unconjugated ASO, ISIS 546254., an unconjugated PKK ASO with the same nucleobase sequence as donidalorsen and uniform phosphodiester (PS) backbone and this approach was accepted by both the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use and the United States (US) FDA. In addition, a 13-week impurity qualification study has been performed in mice, and a 13-week juvenile mouse study was conducted (pending final report) to support a clinical study which will be presented to the Health Authority in a future supplemental new drug application (sNDA) to expand the indication to paediatric patients between 2 to < 12 years of age. The safety pharmacology studies of donidalorsen were conducted including an *in vitro* hERG assay and a single-dose study in monkeys to evaluate the potential effects on cardiovascular, respiratory, and central nervous system (CNS) function.

Key safety findings from toxicity studies and their relevance to human usage of donidalorsen are provided in the Table 2.2-1.

| **Table 2.2-1 Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage** | |
|---|---|
| **Key Safety Findings (from Non-clinical Studies)** | **Relevance to Human Usage** |
| **Single-dose Toxicity**<br>A single-dose safety pharmacology study in the monkey (cardiovascular, neurobehavioral and pulmonary assessment, renal) was performed. No mortality or severe toxicity was noted in monkeys at a dose of up to 30 mg/kg. Additionally, donidalorsen did not block the hERG current in HEK-293 cells at concentrations up to 300 µM. | The results of safety pharmacology study across multiple organ systems, including the cardiovascular, central nervous, pulmonary, and renal systems showed no relevance to humans. |
| **Repeat-dose Toxicity**<br>In multiple repeat dose toxicology studies, donidalorsen produced findings consistent with those expected for 2′-MOE-modified ASOs (Henry et al. 2008).[36] In mice, no adverse effects were observed at doses up to 10 mg/kg/week or 12 mg/kg every two weeks for 13 or 26 weeks of treatment. The NOAEL in mice was determined to be 12 mg/kg every two weeks (24 mg/kg/month), providing ≥ 4.8-fold safety margin compared to the human monthly or every-8-week dose of 80 mg donidalorsen. In monkeys, donidalorsen was well tolerated up to the highest tested doses of 30 mg/kg/week and 12 mg/kg/week over 13 and 39 weeks, respectively, with no signs of overt toxicity, except for sporadic severe reductions in platelet counts in two monkeys at these doses. The NOAEL in monkeys was determined to be 6 mg/kg/week (24 mg/kg/month), offering approximately a 29- to 58-fold cumulative safety margin based on plasma AUC exposure compared to the human dose. Monkeys are considered the most relevant species for the safety evaluation of ASOs. | The toxicities noted in mice were generally related to the pharmacological activity of donidalorsen. These findings are considered as having no relevance to humans as the margins of exposure were approximately ≥ 4.8-fold safety higher than the systemic exposure (AUC) in patients receiving the recommended dose. Platelet reductions observed in animal studies have no relevance to humans in terms of safety risk because these reductions were observed only at a dose approximately 29-58-fold higher than the recommended clinical dose. |
| **Effects on Liver**<br>Differences in liver concentrations between species suggest that mice are more sensitive to hepatotoxicity (e.g., increased ALT) than primates. This sensitivity may be due to the inflammatory effects of donidalorsen observed at high doses in mice (Krieg, 2001; Monteith et al., 1997).[37,38] Mild hepatic toxicity was seen in mice treated with 10 mg/kg/week (40 mg/kg/month) or 12 mg/kg/q2w (24 mg/kg/month), but no hepatotoxicity was detected in mice treated with 4 mg/kg/week (16 mg/kg/month) or 4 mg/kg/q2w (8 mg/kg/month) for up to 26 weeks, or in monkeys treated with doses up to 12 mg/kg/week (48 mg/kg/month) for up to 39 weeks. Monkeys are considered the most relevant species for human safety evaluation. Studies up to 39 weeks in monkeys established appropriate safety margins. The NOAEL in monkeys is 6 mg/kg/week (24 mg/kg/month; cumulative AUC0-48h = 150.4 µgh/mL), which provides a 29- to 58-fold higher safety margin compared to the monthly or every-8-week clinical dose of 80 mg donidalorsen (AUC0-τ: 5.24 µgh/mL) based on cumulative AUC exposure. | The non-clinical findings of mild hepatotoxicity in mice at the dose of 40 mg/kg/month or 24 mg/kg/month are considered not relevant to humans because this toxicity was observed at a very high exposure level compared to clinical dose. In addition, mice are more sensitive to hepatotoxic effects of donidalorsen than primates. Monkeys are considered the more relevant species for human safety evaluation and no human relevant hepatotoxicity was observed in monkey. |

| **Table 2.2-1 Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage** | |
|---|---|
| **Key Safety Findings (from Non-clinical Studies)** | **Relevance to Human Usage** |
| **Effects on Kidney**<br>The kidney was a key organ for donidalorsen uptake and distribution following subcutaneous (SC) administration. After 13 weeks of treatment, donidalorsen concentrations in mice and monkeys reached steady-state levels, with no progression of toxicity observed once these levels were achieved. High-dose groups showed microscopic findings of cytoplasmic basophilic granules in tubular epithelial cells and tubular vacuolation without degeneration or necrosis, which were considered related to the test article but not adverse. These changes did not affect organ function and were reversible after a 13-week recovery period, aligning with steady-state tissue kinetics. Basophilic granules, indicating ASO uptake and accumulation in tissues, were stained with hematoxylin (Butler et al., 1997).[39] These granules in the liver and kidney signify high compound exposure but are not considered toxicologically significant or adverse (Henry et al., 2008; Lenz et al., 2018).[36,40] | These nonclinical observations were considered not relevant to humans as a safety concern, because these findings were not considered toxicologically significant or adverse in animals. |
| **Effects on platelet count and hematology**<br>Hematology parameters in mice remained normal at doses up to 10 mg/kg/week for 13 weeks or 12 mg/kg/q2w for 26 weeks. In monkeys, donidalorsen caused thrombocytopenia (PLT < 25 × 10^9/L) in one female monkey at 12 mg/kg/week on Day 65 and one male at 30 mg/kg/week on Day 80, with reversibility upon steroid treatment or dosing holiday. No PLT reductions were seen in other monkeys up to 12 mg/kg/week in the 39-week study. Similar PLT changes have been noted in monkeys treated with 2′-Methoxyethyl (MOE) ASOs, likely due to increased PLT clearance, possibly in the spleen, without evidence of bone marrow toxicity or thrombosis. Anti-platelet factor 4 (PF4) or anti-PLT antibodies were not implicated in the PLT decrease. The PLT changes in monkeys were reversible upon intervention and did not raise significant safety concerns, with a wide safety margin between monkey NOAEL and clinical doses. | The risk of thrombocytopenia in patients is considered minimal given that the PLT changes seen in monkeys were reversible and there was a wide safety margin between monkey NOAEL and clinical doses, showing minimal human relevance at clinically administered doses.<br><br>Clinical trials with every 4 week donidalorsen dosing up to 100 mg have not shown thrombocytopenia (PLT ≤ 50 × 10^3/µL), consistent with integrated safety data from Phase 2 studies with GalNAc-conjugated 2'-MOE ASOs. |
| **Effects on Complement Activation and Clotting Parameters**<br>The activation of the alternative complement pathway by 2′-MOE ASOs is recognized as a class effect in monkeys but is not observed in humans or other species. Donidalorsen induces transient complement activation in monkeys due to reversible binding of plasma proteins, notably Factor H, to high oligonucleotide concentrations. This effect, consistent across various oligonucleotide sequences, results in elevated plasma complement split product Bb levels, peaking at 4 hours post-dose and returning to baseline by 24 hours. Minimal to mild | There is minimal relevance to patients given the high doses required for activation and lack of sustained coagulation changes in long term studies. Concentration of donidalorsen required for this effect will not be reached at clinical doses. |

| **Table 2.2-1 Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage** | |
|---|---|
| **Key Safety Findings (from Non-clinical Studies)** | **Relevance to Human Usage** |
| perivascular/vascular inflammation was observed in a few monkeys, attributed to ASO-induced complement activation, which is more pronounced in monkeys than in humans. Activation is driven by plasma oligonucleotide Cmax, with significant effects observed at doses ≥ 12 mg/kg/week in monkeys, far exceeding levels seen in clinical doses for humans. Coagulation changes, such as transient prolongations in aPTT, were noted at higher doses but resolved over time and had wide safety margins compared to clinical doses. | |
| **Measurement of Anti-donidalorsen Antibody**<br>Anti-drug antibody (ADA) presence against donidalorsen was evaluated in subchronic and chronic repeated dose studies in monkeys using a validated ELISA assay. Antibodies were detected across all dose groups at Days 91 or 273 assessments, with incidence rates ranging from 12.5% to 62.5% over a dose range of 2 to 12 mg/kg/week (Study No. 721744- AS02PK). To assess the impact on safety parameters, animals were stratified based on immunogenicity (IM) status, comparing positive versus negative animals.<br>Following up to 39 weeks of treatment, little to no consistent differences were observed in donidalorsen exposure, indicated by Cmax or AUC0-48h, between IM-negative and IM-positive animals. Although Cmax values were approximately 70% lower in IM-positive animals after 39 weeks, this difference was not statistically significant. The presence of anti-donidalorsen antibodies resulted in increased plasma trough concentrations, yet tissue levels and terminal elimination half-life values of donidalorsen remained similar between IM-negative and IM-positive animals. Moreover, PLT counts, hepatic PKK mRNA levels, and microscopic findings showed no notable differences between the two groups after 39 weeks of treatment. No apparent correlation between immunogenicity and toxicology or efficacy endpoints was observed. Therefore, immunogenicity had minimal to no effects on PK parameters, efficacy, and toxicity findings in this study. | No effects related to immunogenicity are expected in patients because no correlation between immunogenicity and toxicology or efficacy endpoints was observed in animals. |

## Conclusion

Overall, the toxicology studies for donidalorsen provided data to define target organ systems and dose-effect relationships and formed the basis for an adequate level of understanding of the potential toxicities of acute and chronic exposure in a therapeutic setting. Effects of donidalorsen were reversible and exhibited no evidence of delayed or

recurring toxicity. In addition, there was no evidence of increased severity of target organ toxicity once steady-state tissue concentrations were achieved. The exposure levels in subchronic/chronic studies (weekly or q2w dose) with donidalorsen were similar, and no new toxicities were observed with donidalorsen. No toxicities associated with pharmacologic reduction of PKK plasma levels were observed. Taken together, the collective data from the repeat-dose mouse and monkey studies demonstrated no undesired effects at clinically relevant exposures.

## 2.3 Module SIII: Clinical Trial Exposure

An integrated safety data analysis forms the basis of safety data for this RMP. The focus of the integrated safety data is mainly on the Phase 2 and Phase 3 randomized, double-blind, placebo-controlled studies conducted with donidalorsen: ISIS 721744-CS5 (hereafter referred to as CS5), in which patients received donidalorsen 80mg once every 4 weeks (or matched placebo) or donidalorsen 80 mg once every 80 weeks (or matched placebo), and ISIS 721744-CS2 (hereafter referred to as CS2), in which patients received donidalorsen 80 mg once every 4 weeks or matched placebo. Additional safety data are included from 2 open-label extension (OLE) studies: ISIS 721744-CS3 (hereafter referred to as CS3), an open-label extension (OLE) to the CS2 study, and ISIS 721744-CS7 (hereafter referred to as CS7), an OLE study which included patients who rolled over from CS5 (OLE Cohort) and an additional group of donidalorsen-naïve patients switched from prior HAE long-term prophylactic therapy (Switch Cohort). Two further supporting Phase 1 studies, ISIS 721744-CS1 (hereafter referred to as CS1) and ISIS 721744-CS9 (hereafter referred to as CS9), included only healthy volunteers and are reported separately in the clinical study reports.

The primary conclusions for the safety of donidalorsen in this RMP are derived from pivotal study CS5. The pivotal efficacy study CS2 was supportive for safety and was 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). A further pooled analysis for the sole purpose of showing total exposure to donidalorsen was generated by pooling exposure from the CS5, CS2, CS3, CS7, CS1, and CS9 studies.

Per the data cut off for Integrated Summary of Safety (19 April 2024), 173 patients with HAE were treated with donidalorsen across the 4 studies (CS5, CS2, CS3, and CS7) providing safety data in this module.

## Clinical Trial Exposure by Duration of Exposure

**Table 2.3-1 SIII.1: Clinical Trial Exposure to Donidalorsen by Duration of Exposure**

| Duration of Exposure | Patients | Person Time (year) |
|---|---|---|
| Indication: Hereditary Angioedema (HAE) | | |
| >0 to <=12 weeks | 3 | 0.48 |
| >12 to 24 weeks | 25 | 9.36 |
| >24 to 36 weeks | 24 | 13.94 |
| >36 to 48 weeks | 39 | 31.62 |
| >48 to 60 weeks | 34 | 35.40 |
| >60 to 72 weeks | 21 | 26.23 |
| >72 to 84 weeks | 9 | 13.35 |
| >84 to 96 weeks | 2 | 3.51 |
| >96 to 108 weeks | 1 | 1.92 |
| >108 to 120 weeks | 0 | 0 |
| >120 to 132 weeks | 0 | 0 |
| >132 to 144 weeks | 1 | 2.71 |
| >144 to 156 weeks | 0 | 0 |
| >156 to 168 weeks | 1 | 3.16 |
| >168 to 180 weeks | 3 | 9.91 |
| >180 to 192 weeks | 6 | 21.40 |
| >192 to 204 weeks | 1 | 3.73 |
| >204 to 216 weeks | 3 | 12.27 |
| >216 weeks | 0 | 0 |
| Total Person time | 173 | 188.99 |

**Table 2.3-2 SIII.2: Clinical Trial Exposure to Donidalorsen by Age Group and Gender**

| | Patients | | Person Time (year) | |
|---|---|---|---|---|
| **Age Group** | **M** | **F** | **M** | **F** |
| Indication Hereditary Angioedema (HAE) | | | | |
| Adolescents (12 to 17 years) | 7 | 4 | 5.90 | 3.00 |
| Adults | | | | |
| 18 to 39 years | 36 | 44 | 38.19 | 56.25 |
| 40 to 64 years | 26 | 51 | 25.09 | 53.94 |
| Elderly People (>=65 years) | 3 | 2 | 4.80 | 1.82 |
| Total | 72 | 101 | 73.98 | 115.01 |
| M= male, F=female | | | | |

**Table 2.3-3 SIII.3: Clinical Trial Exposure to Donidalorsen by Dose**

| Dose of Exposure | Patients [1] | Person Time (year) |
|---|---|---|
| Indication: Hereditary Angioedema (HAE) | | |
| 80 mg Every 4 Weeks | 156 | 148.18 |
| 80 mg Every 8 Weeks | 31 | 34.91 |

| **Table 2.3-3 SIII.3: Clinical Trial Exposure to Donidalorsen by Dose** | | |
|---|---|---|
| **Dose of Exposure** | **Patients [1]** | **Person Time (year)** |
| 100 mg Every 4 Weeks | 3 | 5.91 |
| Total Person time | 190 | 188.99 |
| [1] For HAE patients who switched dose levels during the OLE study, they are counted in all dose levels that they were exposed to. | | |

| **Table 2.3-4 SIII.4: Clinical Trial Exposure to Donidalorsen by Ethnic Origin** | | |
|---|---|---|
| **Ethnic Origin** | **Patients** | **Person Time (year)** |
| Indication Hereditary Angioedema (HAE) | | |
| Hispanic or Latino | 10 | 10.40 |
| Not Hispanic or Latino | 163 | 178.59 |
| Total | 173 | 188.99 |
| *Across all treatment groups, the majority of patients were White (93.3%, 95.7%, and 81.8% for the donidalorsen 80 mg Q4W, donidalorsen 80 mg Q8W, and placebo groups, respectively). | | |

## 2.4 Module SIV: Populations Not Studied in Clinical Trials

### 2.4.1 SIV.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Safety related Exclusion Criteria in the donidalorsen clinical program, reason for these exclusions and rationale for not considering these as Missing Information are provided below in the Table 2.4.1-1.

| **Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Donidalorsen Pivotal Study** | | | |
|---|---|---|---|
| **Exclusion Criteria** | **Reason for Exclusion** | **Is it considered to be included as missing information?** | **Rationale** |
| **Platelet count < 130,000/mm$^3$ at baseline**<br>Patients with a history of acquired coagulopathies or bleeding diathesis and inherited bleeding disorders and hypercoagulability were excluded. | These patients were excluded to avoid factors that may confound a complete understanding of the safety profile of donidalorsen. | No | Decreased platelet counts were observed in some patients treated with donidalorsen in clinical studies. These decreases were generally transient, did not lead to any clinically relevant bleeding events and generally resolved while on continued treatment with donidalorsen. No patients reported severe reduction in platelet counts, met the study protocol stopping rules for reduction in platelet count or discontinued from the treatment due to decrease in platelets. No scientific rationale is evident to suspect that the safety profile in this |

| **Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Donidalorsen Pivotal Study** | | | |
|---|---|---|---|
| **Exclusion Criteria** | **Reason for Exclusion** | **Is it considered to be included as missing information?** | **Rationale** |
| | | | patient population may differ to that characterized so far for general patient population. |
| **Renal Impairment**<br>Patients with renal insufficiency as defined below were excluded from the pivotal studies of donidalorsen:<br>For patients ≥ 18 years old: Estimated glomerular filtration rate < 45 mL/min<br><br>For patients 12 and < 18 years old: Estimated glomerular filtration rate<br>< 60 mL/min<br><br>(as determined by the CKD-EPI formula for creatinine clearance) | These patients were excluded to avoid factors that may confound a complete understanding of the safety profile of donidalorsen. | No | No clinically relevant renal impairment TEAEs or abnormal renal function tests were observed with donidalorsen.<br>The mean fraction of unchanged ASO eliminated in urine was less than 1% of the administered dose in healthy subjects within 24 hours indicating that renal excretion is not the major pathway for elimination of donidalorsen. Therefore, there is no scientific rationale to suspect that the safety profile in patients with renal impairment may differ to that characterized so far for general patient population. |
| **Hepatic Impairment**<br>The following liver function tests abnormalities were exclusionary:<br>Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)<br>> 3 ×<br>upper limit of normal (ULN)<br>and Total bilirubin<br>> 1.5 × ULN OR,<br>> 5 mg/dL if due to Gilbert's syndrome | These patients were excluded to avoid factors that may confound a complete understanding of safety profile of donidalorsen. | No | No clinically meaningful hepatic impairment/elevations in liver enzymes were observed with donidalorsen. The overall metabolism of donidalorsen observed in clinical studies was similar to metabolism observed in nonclinical species. While donidalorsen was extensively distributed to the liver in animal studies, no human relevant hepatotoxicity was observed. |
| Malignancy within the last 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated | These subjects were excluded to limit the impact of other active malignancies which may interfere with | No | No cases of fatal, serious or severe malignancies considered related to donidalorsen (by the investigator) were reported. Further characterisation of this population is not feasible due to low prevalence of HAE. However, based on known |

| **Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Donidalorsen Pivotal Study** | | | |
|---|---|---|---|
| **Exclusion Criteria** | **Reason for Exclusion** | **Is it considered to be included as missing information?** | **Rationale** |
| | appropriate evaluation of safety and PK of donidalorsen. | | mechanism of action of donidalorsen, no evidence of increased incidence of chromosomal abnormalities and carcinogenicity assessment in animal studies, this criterion is not relevant for inclusion as missing information. |
| Pregnancy | Pregnant women were excluded from the clinical studies and contraception for female study participants and female partners of male study participants were required because the effects of donidalorsen in pregnant women, fetus and babies are unknown | Yes | Not applicable |
| Breastfeeding | Breastfeeding women were excluded from the clinical studies because the effects of donidalorsen in babies nursed on their mother's milk are unknown | Yes | Not applicable |

### 2.4.2 SIV.2: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

### 2.4.3 SIV.3: Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

**Table 2.4.3-1 Exposure of Special Populations Included or not in Clinical Trial Development Programmes**

| Type of Special Population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development programme |
| Breastfeeding women | |
| Patients with relevant comorbidities:<br>• Patients with moderate to severe hepatic impairment<br>• Patients with moderate to severe renal impairment | Not included in the clinical development programme |
| Population with relevant different ethnic origin | Across all treatment groups, the majority of patients were White (93.3%, 95.7%, and 81.8% for the donidalorsen 80 mg Q4W, donidalorsen 80 mg Q8W, and placebo groups, respectively), however, there are no racial/ethnic differences in prevalence of HAE. |
| Subpopulations carrying relevant genetic polymorphisms | No specific genetic testing was performed for subgroups in the clinical studies. |

## 2.5 Module SV: Postauthorisation Experience

### 2.5.1 SV.1: Postauthorisation Exposure

Donidalorsen is currently not marketed in any country worldwide.

## 2.6 Module SVI: Additional EU Requirements for the Safety Specification

**Potential for Misuse for Illegal Purposes**

Donidalorsen is an ASO, targeting prekallikrein as a therapeutic target and has no potential for misuse for illegal purposes.

## 2.7 Module SVII: Identified and Potential Risks

### 2.7.1 SVII.1: Identification of Safety Concerns in the Initial RMP Submission

#### 2.7.1.1 SVII.1.1: Risk Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

**Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:**

**Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**

- **Injection site reactions (including but not limited to site erythema, injection site discolouration, injection site pain, and injection site pruritus)**

  Injection site reactions are a known risk with administration of donidalorsen.

  Across all donidalorsen clinical studies in patients with HAE, the overall frequency of patients who experienced injection site reactions with donidalorsen was 26.0%. A greater proportion of patients in the donidalorsen 80 mg Q4W (28.2%) experienced injection site reactions compared with the donidalorsen 80 mg Q8W (6.5%) group and the placebo group (7.1%). As expected, the incidence of the injection site reactions was greater in the OLE studies (CS3 and CS7) compared with the CS5 and CS2 studies, consistent with the longer duration of exposure and increased number of injections in these patients. The most frequent injection site reactions observed in all treatment groups were injection site erythema, injection site discolouration, injection site pain, and injection site pruritus. All reactions were nonserious, mild or moderate in severity, and generally self-limiting, and did not result in action taken with study drug or require treatment.

  **Conclusion**

  Based on this data, injection site erythema, injection site discolouration, injection site pain, and injection site pruritus are not considered important for inclusion in the list of safety concerns in the RMP of donidalorsen.

**Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):**

- **Hypersensitivity including Anaphylaxis**

  Across all donidalorsen clinical studies in patients with HAE, 6 hypersensitivity events were reported in 3 patients (1.6%). Among these, one event (0.6%) was classified as serious and met Sampson's criteria for anaphylaxis,[41] while the remaining five events were non-serious. Hypersensitivity events were reported in patients receiving donidalorsen 80 mg Q4W, with symptoms including rash, swollen tongue, urticarial patches, chest discomfort, and tingling sensations. Most of these events were mild to moderate in severity, self-limiting, and resolved without requiring specific treatment or adjustments to the study drug. However, two of these hypersensitivity events, reported in a single serious case, resulted in permanent discontinuation of donidalorsen administration.

  No hypersensitivity reactions were observed in nonclinical studies, and no cases have been reported in the literature for donidalorsen. Preventive measures, such as routine premedication, are not considered necessary due to the low incidence and predominantly mild nature of these events. This risk will be monitored using routine pharmacovigilance measures and risk minimisation through, SmPC (Section 4.3, Section 4.4 and Section 4.8) and the Package Leaflet (PL) Section 2 and 4.

  **Conclusion**

  Based on the above, hypersensitivity including anaphylaxis has been classified as an identified risk, not important for inclusion in the list of safety concerns in the RMP.

### 2.7.1.2 SVII.1.2: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

**Important Identified Risks**

There are no identified risks considered important for donidalorsen.

**Important Potential Risk: Hepatotoxicity**

The risk of hepatotoxicity has been added to the RMP Summary of Safety Concerns because 25 cases with 49 events related to increased hepatic enzymes were observed in the clinical program of donidalorsen. Although most of these events were mild or moderate, isolated, transient in nature, considered unrelated by the investigator and were confounded by pre-existing or concurrent medical conditions and concomitant

medications, the Applicant considers this risk needs further characterization over longer term exposure to donidalorsen.

**Risk-Benefit Impact**

Most hepatic events were nonserious, mostly mild in severity, no cases met Hy's law criteria, and no pattern suggestive of drug-induced liver injury was identified. In 21 out of 25 cases (84%), the causal association was confounded by pre-existing medical conditions, concurrent conditions or concomitant medications. The benefit risk profile of donidalorsen remains favourable for the treatment of HAE.

This risk will be monitored using post marketing routine pharmacovigilance measures such as AE reporting and aggregate reports.

**Important Potential Risk: Renal Toxicity**

The risk of renal toxicity has been added to the RMP Summary of Safety Concerns, as there is limited safety data available on the use of donidalorsen in patients with HAE at the time of marketing authorization. Adverse effects, such as renal toxicity, which have been observed with other antisense oligonucleotides, were not observed during the clinical development of donidalorsen. However, these risks cannot be completely ruled out due to the limited data available.

**Benefit-Risk Impact**

No correlation between renal toxicity and safety parameters has been identified in the clinical studies of donidalorsen. This risk will be monitored using post marketing routine pharmacovigilance measures such as AE reporting and aggregate reports.

**Important Potential Risk: Bleeding/Thrombocytopenia**

The risk of bleeding/ thrombocytopenia has been added to the RMP Summary of Safety Concerns because there is limited safety data available on the use of donidalorsen in patients with HAE at the time of marketing authorization. Although adverse effects, such as bleeding/ thrombocytopenia, have been observed with some antisense oligonucleotides, these events were not observed during the clinical development of donidalorsen. However, they cannot be completely ruled out due to the limited data available.

**Benefit-Risk Impact**

No correlation has been identified between thrombocytopenia and safety parameters in donidalorsen clinical studies. This risk will be monitored using post marketing routine pharmacovigilance measures such as AE reporting and aggregate reports.

**Missing Information: Use in Pregnancy**

**Benefit-Risk Impact:**

Patients who were pregnant were excluded from participating in clinical trials in order to avoid potential harm to the unborn foetus. Women of childbearing potential were required to use highly effective contraceptive methods and negative pregnancy tests were required during screening and prior to dosing of donidalorsen. Therefore, no data on the use of donidalorsen during pregnancy is available. However, nonclinical studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Safety profile in this population is not known, hence use in pregnancy is considered as missing information. Post-marketing data obtained via routine pharmacovigilance activities will be utilized to further characterize the safety profile of donidalorsen in this population.

**Missing Information: Use during Breastfeeding**

**Benefit-Risk Impact:**

Patients who were breastfeeding their babies were excluded from participating in clinical trials to avoid potential harm to breastfed infants.

It is not known whether donidalorsen is excreted in human milk or has effects on the breastfed infant or milk production. For these reasons, the recommendation is that a benefit assessment should be undertaken to determine whether donidalorsen therapy is discontinued during breastfeeding.

Safety profile in this population is not known, hence use during breastfeeding is considered as missing information. Post-marketing data obtained via routine pharmacovigilance activities will be utilized to further characterize the safety profile of donidalorsen in this population.

**Missing Information: Long Term Use**

Donidalorsen is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older. At the time of submission, based on the data cut off for this RMP, 173 patients with HAE have been treated with donidalorsen. The available safety data are limited both in terms of numbers

and extent of follow-up. Therefore, long-term safety of donidalorsen has not yet been sufficiently well characterized.

### 2.7.2 SVII.2: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not Applicable.

### 2.7.3 SVII.3: Details of Important Identified Risks, Important Potential Risks, and Missing Information

#### 2.7.3.1 SVII.3.1: Presentation of Important Identified Risks and Important Potential Risks

##### 2.7.3.1.1 Important Potential Risk: Hepatotoxicity

**Potential mechanisms**

The mechanism(s) of potential hepatotoxicity with donidalorsen is unknown, however, some possible mechanisms for hepatotoxicity with ASOs in general are proposed below:

- Studies suggest that some hepatotoxicity is linked to the interaction of oligonucleotides with RNase H1.[42]
- Modifications like locked nucleic acids, while enhancing binding affinity and stability, can also contribute to hepatotoxicity[43] (unlikely with donidalorsen due to different chemistry).
- The specific sequence of the oligonucleotide can influence its potential to cause liver toxicity, highlighting the importance of careful design.[44]
- Even impurities within oligonucleotide drugs can contribute to hepatotoxicity, emphasizing the need for strict quality control in manufacturing.[45]

However, a comparative analysis by Baker et al. (2023)[46] examined the safety and tolerability of GalNAc-conjugated 2'MOE ASOs relative to their unconjugated counterparts, and found that GalNAc-conjugated 2'MOE ASOs, such as donidalorsen has an improved hepatotoxicity profile as compared to its unconjugated counterparts.

**Evidence source(s) and strength of evidence:**

Across the clinical programme of donidalorsen, 25 cases with 49 events related to increased hepatic enzymes were observed. The majority of these cases were confounded by pre-existing medical conditions and concomitant conditions such as diabetes mellitus, thalassaemia beta, hypertransaminasaemia, hypothyroidism, polycystic ovarian syndrome, Lyme disease, hepatic steatosis, obesity, hypercholesterolaemia, and infections. The majority of these patients also reported polypharmacy (paracetamol, antibiotics, and statins) which is an additional risk factor for elevated liver enzymes.

**Characterization of the risk:**

Across 4 clinical studies, 49 events related to increased hepatic enzymes were observed in 25 patients. All events were nonserious. The majority of events were mild in severity (41 of 49 events [83.7%]) and a few were moderate (8 of 49 events [16.3%]). Importantly, no cases met Hy's law criteria, and no pattern suggestive of drug-induced liver injury was identified. In 21 out of 25 cases (84%), the causal association was confounded by pre-existing medical conditions, concurrent conditions or concomitant medications.

Based on mechanism of action, nonclinical data, and clinical data, donidalorsen doesn't appear to impact liver function. However, limited data on number of patients and duration of exposure is available at this time and this risk needs further characterisation.

**Risk factors and risk groups:**

Alcohol consumption, underlying comorbidities such as type 2 diabetes, Metabolic Dysfunction-Associated Steatohepatitis (MASH), hepatitis, autoimmune diseases, exposure to hepatotoxins or hepatotoxic materials/drugs, malnutrition, and herbal supplements not approved by healthcare provider.

**Preventability:**

Avoidance of risk factors.

**Impact on the benefit-risk balance of the product:**

Most hepatic events were nonserious, mostly mild in severity, no cases met Hy's law criteria, and no pattern suggestive of drug-induced liver injury was identified. In 21 out of 25 cases (84%) the causal association was confounded by pre-existing medical conditions, concurrent conditions or concomitant medications. Based on the current available data no negative impact on the benefit-risk is expected.

**Public health impact:**

As the impact is to the treated population of patients with HAE only, there is no public health impact.

### 2.7.3.1.2 Important Potential Risk: Renal Toxicity

**Reasons for inclusion:**

There are limited safety data available on the use of donidalorsen in patients with HAE at the time of marketing authorisation. Adverse effects observed after the administration of some antisense oligonucleotides, including renal toxicity, were not observed during

clinical development of donidalorsen but cannot be completely excluded due to limited data available to date; therefore, renal toxicity was added as important potential risks to the RMP.

**Potential mechanisms:**

The exact mechanism is currently unknown.

**Evidence source(s) and strength of evidence:**

Donidalorsen has not been associated with renal toxicity based on completed chronic renal toxicology studies in non-human primates.

Donidalorsen was not associated with renal toxicity during clinical trials including completed and ongoing open-label extension studies.

**Characterisation of the risk:**

Renal toxicity adverse effects were identified using MedDRA search criteria: SMQ Acute renal failure (broad and narrow). Clinical studies show a low incidence of renal-related treatment-emergent adverse events (TEAEs), which were mostly mild, non-serious, and often unrelated to treatment. No renal TEAEs led to discontinuation of treatment or met the protocol specified stopping criteria. Renal function markers (eGFR, serum creatinine, BUN, urine protein) remained generally within normal ranges, with only transient and isolated changes observed.

Across all HAE trials, 6 patients (3.4%) with 6 events were reported for renal effect. Of these 6 events, 5 events were not related and 1 event (0.6%) of blood creatinine increased was related to donidalorsen. All events were nonserious and mild in severity (6 of 6 events [3.4%]).

No patient experienced a serious renal toxicity event or was permanently discontinued from study drug due to a renal toxicity event.

Safety data do not suggest that donidalorsen treatment has a clinically meaningful impact on renal function.

**Risk factors and risk groups:**

Underlying cardiac and renal comorbidities, dehydration, diabetes mellitus, infections, and nephrotoxic medications.

**Preventability:**

Avoidance of known risks factors such as nephrotoxic medications and routine laboratory testing as per standard of care.

**Impact on the risk- benefit balance of the product:**

No correlation has been identified between renal toxicity and safety parameters in donidalorsen clinical studies.

**Public health impact:**

As the impact is to the treated population of patients with HAE only, there is no public health impact.

#### 2.7.3.1.3 Important Potential Risk: Bleeding/Thrombocytopenia

**Reasons for inclusion:**

There are limited safety data available on the use of donidalorsen in patients with HAE at the time of marketing authorisation. Adverse effects observed after the administration of some antisense oligonucleotides, including bleeding/ thrombocytopenia, were not observed during clinical development of donidalorsen but cannot be completely excluded due to limited data available to date and are therefore added as important potential risks to the RMP.

**Potential mechanisms:**

Thrombocytopenia or interference with coagulation has been observed with some antisense oligonucleotides.

An extensive investigation to evaluate the potential cause of thrombocytopenia/ platelet count changes has been conducted with unconjugated ASOs, however, donidalorsen is a conjugated 2′-MOE ASO).

No serious risk of thrombocytopenia or interference with coagulation was identified during clinical development with donidalorsen.

**Evidence source(s) and strength of evidence:**

Donidalorsen has not been associated with thrombocytopenia or interference with coagulation based on completed chronic toxicology studies in non-human primates.

No patient met the predefined stopping rule regarding platelet counts, or discontinued treatment due to a thrombocytopenia TEAE, and no patient with platelet count < LLN experienced a concurrent serious or severe bleeding event.

**Characterisation of the risk:**

Events of thrombocytopenia and bleeding were identified by the following search criteria:

PT: Thrombocytopenia.

PT: Platelet count decreased

Bleeding TEAEs were identified based on the Haemorrhages (Standardized MedDRA Queries

[SMQ]) broad search export from MedDRA.

Across HAE population studies, no TEAEs of thrombocytopenia were observed.

No patient treated with donidalorsen experienced a platelet count of < 50,000/$mm^3$. Across all HAE trials, 2 patients (1.2%) with 3 events were reported for platelet count decreased. All 3 events were assessed as non-serious and related to donidalorsen. The severity of 2 events was moderate (66.7%), and one event was mild (33.3%).

Across all HAE trials, 32 patients (18.1%) with 52 events reported for bleeding. All events were nonserious except 1 serious event of epistaxis which was considered not related to the study treatment by the investigator. The majority of the events were mild in severity or moderate. No event met the predefined stopping rule to discontinue the study treatment.

**Risk factors and risk groups:**

Patients with thrombocytopenia < 100 × $10^9$/L and pre-existing coagulation abnormalities.

**Preventability:**

As the impact is to the treated population of patients with HAE only, there is no public health impact.

**Impact on the risk- benefit balance of the product:**

No correlation has been identified between thrombocytopenia and safety parameters in donidalorsen clinical studies.

**Public health impact:**

As the impact is to the treated population of patients with HAE only, there is no public health impact.

### 2.7.3.2 SVII.3.2: Presentation of the Missing Information

#### 2.7.3.2.1 Use in Pregnancy

**Evidence source:**

Clinical trials excluded pregnant women; therefore, there are no adequate data from the use of donidalorsen during pregnancy.

The mean age of patients at onset of symptoms of HAE is 12.6 years.[10] HAE affects both genders equally. Many female patients with HAE are of childbearing potential which may lead to potential exposure to donidalorsen in pregnancy. The potential risks of donidalorsen to pregnant patients are unknown, hence, this population needs further characterization of the risks.

Donidalorsen showed no adverse effects on fertility (male and female), reproductive performance, and developmental toxicity, including teratogenic potential in mice. In addition, there was no effect of PKK mRNA inhibition on reproduction, uterine implantation, fetal body weight, fetal sex ratio or fetal external, visceral or skeletal examinations, as examined with the mouse-surrogate. Fertility and embryo-fetal development studies were also previously completed for the unconjugated parent ASO, ISIS 546254, which has the same sequence and chemistry (2′MOE phosphorothioate-modified) as donidalorsen, but with a different backbone. ISIS 546254 did not produce any changes in fertility in male or female mice nor any effects on embryo-fetal development in mice at clinically relevant doses. An embryo-fetal developmental toxicity study was also conducted in rabbits, and no adverse changes were seen in embryo-fetal development at doses of ISIS 546254 up to 75 mg/kg/wk (Study No. 546254-AS05).

**Population in need of further characterisation:**

Data regarding the use of donidalorsen in pregnant individuals are limited. Given the potential risks to maternal and fetal health, further information is needed to characterize safety in these populations.

#### 2.7.3.2.2 Use during Breastfeeding

**Evidence Source:**

Clinical trials excluded women who were breastfeeding their babies; therefore, there are no adequate data from the use of donidalorsen during breastfeeding.

The potential risks of donidalorsen to breastfed neonates are unknown, hence, this population needs further characterization of the risks.

It is not known whether donidalorsen or its metabolites are excreted in human milk or have effects on a breastfed infant or milk production. Although donidalorsen was detected in animal milk, any systemic exposure in pups is unlikely due to the lack of oral absorption of 2′-MOE ASOs. The mouse surrogate, ISIS 722059, also showed no effect on pre- and postnatal development.

**Population in need of further characterisation:**

Data regarding the use of donidalorsen during breastfeeding are currently lacking. The potential risks to breastfed neonates remain unknown, hence, further information is needed to characterize safety in this population.

#### 2.7.3.2.3 Long-term use

**Evidence Source:**

As of the data cut-off date for the MAA, 173 subjects were enrolled in clinical studies, of whom only 72 had been treated for more than one year. Within this subset, it is estimated that approximately 60 patients had received the proposed 80 mg monthly dose for over 12 months.

**Anticipated risk/consequence of the missing information:**

The primary risk associated with the limited data on long-term use is the potential emergence of unanticipated adverse events, including rare, cumulative, or delayed safety concerns, which may not yet be evident due to the relatively short follow-up period for a majority of patients. This lack of sufficient data for extended treatment duration may result in an incomplete understanding of the safety profile, thus impacting the ability to fully evaluate the long-term risk-benefit balance of donidalorsen.

## 2.8 Module SVIII: Summary of the Safety Concerns

**Table 2.8-1 SVIII-1: Summary of Safety Concerns**

| | |
|---|---|
| **Important Identified Risks** | • None |
| **Important Potential Risks** | • Hepatotoxicity<br>• Renal toxicity<br>• Bleeding/Thrombocytopenia |
| **Missing Information** | • Use in pregnancy<br>• Use during breastfeeding<br>• Long-term use |

# 3 PART III: PHARMACOVIGILANCE PLAN (Including Post-authorisation Safety Studies)

## 3.1 III.1: Routine Pharmacovigilance Activities

**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

There are no routine pharmacovigilance activities beyond adverse reactions reporting, and signal detection.

## 3.2 III.2: Additional Pharmacovigilance Activities

An ongoing open-label long-term study ISIS 721744-CS7 has been included as an additional pharmacovigilance activity, aiming to provide further characterization of the safety concerns.

**Study short name and title:**

ISIS 721744-CS7: An Open-Label, Long Term Safety and Efficacy Study of Donidalorsen in the Prophylactic Treatment of Hereditary Angioedema (HAE). (EudraCT No: 2022-000757-93)

**Rationale and study objectives:**

Rationale:

There are limited safety data available on the use of donidalorsen in patients with HAE at the time of marketing authorisation. Adverse effects observed after the administration of some antisense oligonucleotides, including bleeding/thrombocytopenia, were not observed during clinical development of donidalorsen but cannot be completely excluded due to limited data available to date and are therefore added as important potential risks to the RMP.

Objectives:

Primary objective: To evaluate the safety of long-term dosing with donidalorsen in patients with HAE.

Secondary objective: To evaluate the long-term efficacy and the effects of donidalorsen on the number of HAE attacks and their impact on the quality of life (QoL) of patients with HAE.

CCI [redacted]

**Study design:**

This study is an Open-Label global study with donidalorsen conducted in multiple centres to evaluate the long-term safety and efficacy of donidalorsen in preventing angioedema attacks in patients with HAE-1 (Type I) and HAE-2 (Type II). There are 2 arms to this study; 1) patients who roll-over from another study of donidalorsen (OLE patients), and 2) donidalorsen treatment naive patients who are not rolling over from another donidalorsen study and were previously maintained on HAE prophylactic therapy ("Switch" patients) with lanadelumab, berotralstat or C1-esterase inhibitor.

**Study population:** Patients aged ≥ 12 years at the time of informed consent with documented diagnosis of HAE-1/HAE-2.

**Duration of Study:**

Qualification period: up to 4 weeks

Treatment Period: Week 1 to Week 53 (52 weeks)

Extended Treatment Period: Week 57 to Week 157 (100 Weeks) *

Follow-up period (part of completion of this study): 13 weeks

(*A protocol amendment has been submitted in September 2025 [awaiting approval] to the European Union to Extended Schedule of Procedures for up to 2 additional years of Extended Treatment Period after Week 157 until Week 261 to allow for collection of additional safety data).

**Milestones:**

The first patient in this study was screened on 14 Jul 2022.

The last patient last visited is planned to be by 31 December 2027

The final study report including analyses of hepatotoxicity, renal toxicity, bleeding/ thrombocytopenia and long term safety is expected to be submitted in December 2028.

**Details on characterization of safety concerns:**

Study CS7 is a global, multicenter, open-label extension designed to evaluate the long-term safety of donidalorsen in patients with hereditary angioedema. The study is designed to generate high-quality and standardized data, facilitating comprehensive characterization of both overall and organ-specific toxicities, and supporting the assessment of temporal and causal relationships, particularly with respect to safety endpoints over extended exposure.

A brief description of how hepatotoxicity, renal toxicity, bleeding/thrombocytopenia and long-term use safety will be characterized with data from Study CS7 is provided below.

### Characterization of Hepatotoxicity

In the CS7 study, hepatotoxicity will be monitored through regular liver chemistry assessments, including ALT, AST, GGT, ALP, bilirubin, and INR, conducted at regular intervals during the Treatment Period and continued thereafter. Abnormal results will trigger prompt review by investigators and medical monitors, with further evaluation including clinical assessment, imaging, or biopsy if indicated. All hepatobiliary adverse events will be documented in detail, including clinical course, laboratory trends, concomitant medications, comorbidities, causality, severity, and seriousness. Analyses will evaluate incidence, severity, relatedness, exposure-adjusted rates, time to event, duration and normalization of abnormalities, and longitudinal trends. These analyses will be provided with the complete study report (expected by December 2028)

### Characterization of Renal Toxicity

In the CS7 study, renal toxicity will be evaluated through regular laboratory monitoring and clinical assessments to capture detailed information on renal-related adverse events. Patients will have renal function tests at regular intervals during the Treatment Period and continued thereafter. All events, including symptoms such as oliguria, edema, fatigue, nausea, hematuria, pruritus, and hypertension, will be documented with information on clinical course, concomitant medications, comorbidities, investigations, outcomes, causality, seriousness, and severity. Analyses similar to hepatotoxicity will be performed but with focus on renal related parameters. These analyses will be provided with the complete study report (expected by December 2028)

### Characterization of Bleeding /Thrombocytopenia

In the CS7 study, patients will be continuously monitored for bleeding events from the start of donidalorsen treatment through the end of follow-up, with all events recorded as adverse events. Platelet counts will be measured at regular intervals during the Treatment Period and continued thereafter. Laboratory monitoring includes complete blood counts, coagulation parameters, and additional tests as clinically indicated, with any relevant abnormalities prompting further evaluation. All events will be assessed for causality with donidalorsen, and analyses will include incidence, severity, time-to-event, and exposure-adjusted rates, with trends in platelet counts and coagulation parameters graphically represented. These analyses will be provided with the complete study report (expected by December 2028). This approach enables comprehensive characterization of the impact of

donidalorsen on platelet count and coagulation and the associated risk of haemorrhagic complications. These analyses will be provided with the complete study report (expected by December 2028).

### Characterization of "Long term use" Safety

Long-term safety will be characterized through continuous monitoring of AEs, SAEs, AESIs, laboratory parameters, vital signs, physical examinations, ECGs, and other clinical assessments as needed throughout the treatment and continued thereafter. Organ-specific safety monitoring in addition to described above for hepatic, renal and bleeding/thrombocytopenia will include all other system organ classes, predefined laboratory thresholds and TEAE or lab parameter driven evaluations triggering additional investigations and clinical interventions as appropriate. All TEAEs will be assessed for severity, relatedness and seriousness.

Analyses will include descriptive summaries of the incidence and severity of AEs, incidence rates per 100 person-years to account for variable exposure durations, time-to-event analyses, and analyses of laboratory parameters to evaluate trends over time.

This comprehensive approach will allow for detailed characterization of delayed, cumulative, or rare toxicities, supporting a thorough evaluation of the long-term safety profile of the donidalorsen in HAE patients.

### Conclusion

In the CS7 study, a rigorous and systematic safety monitoring framework is employed, encompassing clinical and laboratory assessments, TEAE collection, pharmacokinetic and pharmacodynamic evaluations, and anti-drug antibody testing. This approach emphasizes both overall adverse events and specific risks, including hepatotoxicity, renal injury, bleeding/thrombocytopenia, and other organ-specific toxicities, thereby ensuring comprehensive and high-quality data collection. All TEAEs and lab abnormalities with specific focus on hepatotoxicity, renal toxicity, and bleeding/thrombocytopenia will undergo a thorough medical review and routine PV. Analyses of TEAEs, lab abnormalities and other safety parameters including incidence, severity, relatedness, exposure-adjusted rates, time-to-event assessments, and trends and patterns. This methodology facilitates a detailed and robust characterization of donidalorsen's organ specific and long-term safety profile, encompassing delayed, cumulative, and possibly rare toxicities with donidalorsen in patients with HAE.

## 3.3 III.3: Summary Table of Additional Pharmacovigilance Activities

**Table 3.3-1 III.3-1: Ongoing and Planned Additional Pharmacovigilance Activities**

| Study Number<br>Title<br>Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 3- Required additional pharmacovigilance activities** | | | | |
| **ISIS 721744-CS7**<br>An Open-Label, Long Term Safety and Efficacy Study of Donidalorsen in the Prophylactic Treatment of Hereditary Angioedema (HAE).<br>**Ongoing** | - Evaluate the safety of long-term dosing with donidalorsen in patients with HAE.<br>- Evaluate the long-term efficacy and the effects of donidalorsen on the number of HAE attacks and their impact on the quality of life (QoL) of patients with HAE.<br>- CCI [redacted] | Long-term use<br>Hepatotoxicity<br>Renal toxicity<br>Bleeding/Thrombocytopenia | Final Report | LPLV: December 2027<br>Final Study Report: Dec 2028 |

# 4 PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies are planned for donidalorsen.

# 5 PART V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

**Risk Minimisation Plan**

## 5.1 V.1: Routine Risk Minimisation Measures

**Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine Risk Minimisation Activities |
|---|---|
| Hepatotoxicity | Routine risk communication: None<br>Other routine risk minimisation measures beyond the Product Information: Prescription only medicine |
| Renal toxicity | Routine risk communication: None<br>Other routine risk minimisation measures beyond the Product Information: Prescription only medicine |
| Bleeding/Thrombocytopenia | Routine risk communication: None<br>Other routine risk minimisation measures beyond the Product Information: Prescription only medicine |
| Use in pregnancy | Routine risk communication: SmPC Section 4.6, Package Leaflet (PL) Section 2<br>Other routine risk minimisation measures beyond the Product Information: Prescription only medicine |
| Use during breastfeeding | Routine risk communication: SmPC Section 4.6, Package Leaflet (PL) Section 2<br>Other routine risk minimisation measures beyond the Product Information: Prescription only medicine |
| Long-term use | Routine risk communication: None<br>Other routine risk minimisation measures beyond the Product Information: Prescription only medicine |

## 5.2 V.2: Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

## 5.3 V.3: Summary of Risk Minimisation Measures

**Table 5.3-1 V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Hepatotoxicity | Routine Risk Minimization measures:<br>Prescription only medicine<br>Additional risk minimization measure:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br><br>Additional pharmacovigilance activities: ISIS 721744-CS7 |
| Renal Toxicity | Routine Risk Minimization measures:<br>Prescription only medicine<br>Additional risk minimization measure:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br><br>Additional pharmacovigilance activities: ISIS 721744-CS7 |
| Bleeding/ Thrombocytopenia | Routine Risk Minimization measures:<br>Prescription only medicine<br>Additional risk minimization measure:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br><br>Additional pharmacovigilance activities: ISIS 721744-CS7 |
| Use in pregnancy | Routine Risk Minimization measures:<br>SmPC Section 4.6<br>PL Section 2<br>Prescription only medicine<br><br>Additional risk minimization measure:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br><br>Additional pharmacovigilance activities: None |
| Use during breastfeeding | Routine Risk Minimization measures:<br>SmPC Section 4.6<br>PL Section 2<br>Prescription only medicine<br><br>Additional risk minimization measure:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br><br>Additional pharmacovigilance activities: None |
| Long-term use | Routine Risk Minimization measures:<br>Prescription only medicine<br>Additional risk minimization measure:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br><br>Additional pharmacovigilance activities: Study ISIS 721744-CS7 |

# 6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## 6.1 VI.1: Summary of the Risk Management Plan for Dawnzera (donidalorsen)

This is a summary of the risk management plan (RMP) for Dawnzera. The RMP details risks of Dawnzera, how these risks can be minimised, and how more information will be obtained about Dawnzera's risks and uncertainties (missing information).

Dawnzera's summary of product characteristics (SmPC) and package leaflet gives essential information to healthcare professionals and patients on how Dawnzera should be used.

This summary of the RMP for Dawnzera should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Dawnzera's RMP.

### 6.1.1 I: The Medicine and What it is Used for

Dawnzera is indicated for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older. It contains donidalorsen as the active substance and it is given as subcutaneous injection.

Further information about the evaluation of Dawnzera's benefits can be found in Dawnzera's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage */* [link to product's EPAR summary landing page on the EMA webpage.]*/*

### 6.1.2 II: Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Dawnzera, together with measures to minimise such risks and the proposed studies for learning more about Dawnzera's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Dawnzera is not yet available, it is listed under 'missing information' below.

#### 6.1.2.1 II.A: List of Important Risks and Missing Information

Important risks of Dawnzera are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Dawnzera. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

**Table 6.1.2.1-1 II.A-1: List of Important Risks and Missing Information**

| | |
|---|---|
| **Important Identified Risks** | None |
| **Important Potential Risks** | • Hepatotoxicity<br>• Renal toxicity<br>• Bleeding/thrombocytopenia |
| **Missing Information** | • Use in pregnancy<br>• Use during breastfeeding<br>• Long-term use |

### 6.1.2.2 II.B: Summary of Important Risks

| Table 6.1.2.2-1 II.B-1: Hepatotoxicity | |
|---|---|
| **Evidence for linking the risk to the medicine** | Across the clinical programme of donidalorsen, 26 cases with 56 events related to increased hepatic enzymes were observed. Most of these cases were confounded by pre-existing medical conditions and concomitant conditions such as diabetes mellitus, thalassaemia beta, hypertransaminasaemia, hypothyroidism, polycystic ovarian syndrome, Lyme disease, hepatic steatosis, obesity, hypercholesterolaemia, and infections. The majority of these patients also reported polypharmacy (paracetamol, antibiotics, and statins), which is an additional risk factor for elevated liver enzymes. However, the Applicant decided to include hepatotoxicity as an important potential risk, until further data is available. |
| **Risk factors and risk groups** | Alcohol consumption, underlying comorbidities such as type 2 diabetes, Metabolic Dysfunction-Associated Steatohepatitis (MASH), hepatitis, autoimmune diseases, exposure to hepatotoxins or hepatotoxic materials/drugs, malnutrition, and herbal supplements not approved by healthcare provider |
| **Risk minimisation measures** | **Routine risk minimisation measures**: Prescription only medicine<br>**Additional risk minimisation measures:** None |
| **Additional pharmacovigilance activity** | Study ISIS 721744-CS7 |

| Table 6.1.2.2-2 II.B-2: Renal Toxicity | |
|---|---|
| **Evidence for linking the risk to the medicine** | Donidalorsen has not been associated with renal toxicity based on completed chronic renal toxicology studies in non-human primates. Donidalorsen was not associated with renal toxicity during clinical trials including completed and ongoing open-label extension studies. |
| **Risk factors and risk groups** | Risk factors that may predispose individuals to renal toxicity include underlying cardiac and renal comorbidities, dehydration, diabetes mellitus, infections, and co-administration of nephrotoxic medications. |
| **Risk minimisation measures** | **Routine risk minimisation measures**: Prescription only medicine<br>**Additional risk minimisation measures:** None |
| **Additional pharmacovigilance activity** | Study ISIS 721744-CS7 |

| **Table 6.1.2.2-3 II.B-3: Bleeding/Thrombocytopenia** | |
|---|---|
| **Evidence for linking the risk to the medicine** | Donidalorsen has not been associated with thrombocytopenia or interference with coagulation based on completed chronic toxicology studies in non-human primates. No patient met the predefined stopping rule regarding platelet counts, or discontinued treatment due to a thrombocytopenia TEAE, and no patient with platelet count < LLN experienced a concurrent serious or severe bleeding event. |
| **Risk factors and risk groups** | Patients with baseline thrombocytopenia (platelet count <100 × $10^9$/L) and pre-existing coagulation abnormalities could be at an increased risk of experiencing adverse events. |
| **Risk minimisation measures** | **Routine risk minimisation measures:** Prescription only medicine<br>**Additional risk minimisation measures:** None |
| **Additional pharmacovigilance activity** | Study ISIS 721744-CS7 |

| **Table 6.1.2.2-4 II.B-4: Use in Pregnancy** | |
|---|---|
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>SmPC Section 4.6<br>PL Section 2<br>Prescription only medicine |

| **Table 6.1.2.2-5 II.B-5: Use during Breastfeeding** | |
|---|---|
| **Risk minimisation measures** | **Routine risk minimisation measures:**<br>SmPC Section 4.6<br>PL Section 2<br>Prescription only medicine |

| **Table 6.1.2.2-6 II.B-2: Long-Term Use** | |
|---|---|
| **Risk minimisation measures** | **Routine risk minimisation measures:** Prescription only medicine<br>**Additional risk minimisation measures**: None |
| **Additional Pharmacovigilance Activities** | Study ISIS 721744-CS7 |

### 6.1.2.3 II.C: Post-authorisation Development Plan

#### 6.1.2.3.1 II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of donidalorsen.

### 6.1.2.3.2 II.C.2 Other Studies in Post-authorisation Development Plan

**Protocol Number: ISIS 721744-CS7 (EudraCT No: 2022-000757-93)**

An Open-Label, Long Term Safety and Efficacy Study of Donidalorsen in the Prophylactic Treatment of Hereditary Angioedema (HAE)

Primary objective: To evaluate the safety of long-term dosing with donidalorsen in patients with HAE.

Secondary objective: To evaluate the long-term efficacy and the effects of donidalorsen on the number of HAE attacks and their impact on the quality of life (QoL) of patients with HAE.

CCI [redacted]

# 7 PART VII: ANNEXES TO THE RISK MANAGEMENT PLAN

## 7.4 Annex 4: Specific Adverse Drug Reaction Follow-up Forms

This annex is not applicable as there are no specific adverse drug reaction follow-up forms.

## 7.6 Annex 6: Details of Proposed Additional Risk Minimisation Activities (if applicable)

This annex is not applicable as there are no additional risk minimisation activities proposed.