EU RISK MANAGEMENT PLAN (RMP)

for

TAKHZYRO® (Lanadelumab)

RMP Version number: 4.0

Date: 27-November-2023

[redacted]

[redacted]

[redacted]

EU Risk Management Plan for TAKHZYRO (Lanadelumab)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 4.0

Data lock point for this RMP: 22-August-2023

Date of final sign off: 27-November-2023

Rationale for submitting an updated RMP:

The RMP is updated as a part of Type II/C.I.4 Variation Application for Takhzyro, to submit both 303 (CASPIAN) and 3001 (CASPIAN OLE) clinical study reports (CSRs) and to remove Takhzyro from the list of products under additional monitoring, as per the European Medicines Agency (EMA) recommendation from renewal procedure EMEA/H/C/004806/R/0035.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	The product is removed from the list of Product under additional monitoring as per the EMA recommendation from renewal procedure EMEA/H/C/004806/R/0035.
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Updated prevalence data.
• **Module SII Non-clinical part of the safety specification**	Not applicable.
• **Module SIII Clinical trial exposure**	Updated clinical exposure to aligned with current DLP.
• **Module SIV Populations not studied in clinical trials**	Not applicable.
• **Module SV Post-authorisation experience**	Updated patient exposure to aligned with current DLP.
• **Module SVI Additional EU requirements for the safety specification**	Not applicable.
• **Module SVII Identified and potential risks**	Not applicable.
• **Module SVIII Summary of the safety concerns**	Not applicable.
Part III Pharmacovigilance plan	Not applicable.
Part IV Plans for post-authorisation efficacy studies	Not applicable.
Part V Risk minimisation measures	Not applicable.
Part VI Summary of the risk management plan	Not applicable.
Part VII Annexes	Not applicable.

[redacted]

[redacted]

Other RMP versions under evaluation:

RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

Details of the currently approved RMP:

Version number:	3.2
Approved with procedure:	EMEA/H/C/004806/X/0034/G
Date of approval (opinion date):	15-November-2023

QPPV name: Stéphane Brouckaert

QPPV signature: [redacted] RMP signatures are kept on file.

Please note that e-signature may also be performed by Deputy EU QPPV [redacted] on behalf of the EU and UK QPPV (i.e., 'per procurationem').

[redacted]

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List of Abbreviations

Abbreviation	Definition/Description
ACE	Angiotensin-Converting Enzyme
ADA	Anti-drug antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	The Anatomical Therapeutic Chemical Classification
AUC	Area Under Curve
C1-INH	C1 inhibitor
CHO	Chinese Hamster Ovary
CI	Confidence Interval
$C_{L/F}$	Apparent plasma clearance
C_{max}	Maximum concentration occurring at t_{max}
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
CSR	Clinical Study Report
CV	Cardiovascular
DILI	Drug-induced liver injury
DLP	Data-lock point
DMID	Division of Microbiology and Infectious Diseases
DNA	Deoxy Ribonucleic Acid
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ePPND	The enhanced pre- and postnatal development
EU	European Union

Abbreviation	Definition/Description
FOB	Functional observational battery
HAE	Hereditary angioedema
HLA	Human leukocyte antigen
HR	Heart rate
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INN	International Non-proprietary Name
IR	Insulin resistance
ISR	Injection site reaction
IV	Intravenous
KKS	Kinin-kallikrein system
mAb	Monoclonal antibody
NAFLD	Non-alcoholic fatty liver disease
NOAEL	No-observed-adverse-effect-level
PD	Pharmacodynamic
PK	Pharmacokinetic
pKal	Active plasma kallikrein
PL	Package leaflet
PSUR	Periodic safety update report
q2w	Every 2 weeks
Q4w	Every 4 weeks
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious Adverse Event
SC	Subcutaneous
SmPC	Summary of Product Characteristic
T2DM	Type 2 diabetes mellitus
TA	Transaminase
TBL	Total bilirubin
TEAE	Treatment-Emergent Adverse Event
TK	Toxicokinetic
ULN	Upper Limit of Normal
$V_{C/F}$	Apparent volume of distribution
WHO	World Health Organisation

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active Substance(s) (INN or common name)	Lanadelumab (TAK743, SHP643, DX-2930)
Pharmacotherapeutic group(s) (ATC Code)	Other haematological agents, drugs used in hereditary angioedema (B06AC05)
Marketing Authorisation Holder:	Takeda Pharmaceuticals International AG Ireland Branch
Medicinal products to which this RMP refers	Lanadelumab
Invented name(s) in the European Economic Area (EEA):	Takhzyro®
Marketing authorisation procedure	Centralized
Brief description of the product	**Chemical class** Lanadelumab is a recombinant, fully human Immunoglobulin G $(IgG)_1$, kappa light chain, monoclonal antibody (mAb) targeted against active plasma kallikrein (pKal).
	Summary of Mechanism of Action Lanadelumab acts on the plasma kallikrein-kinin pathway and is a potent and specific inhibitor (Ki=125 pM) of the proteolytic activity of active plasma kallikrein. Lanadelumab inhibits active plasma kallikrein proteolytic activity without binding prekallikrein, the inactive precursor found in the circulation. As lanadelumab has a long half-life (approximately 14 days in patients with hereditary angioedema [HAE]), treatment with lanadelumab has the potential to provide sustained control of pKal and thereby limiting bradykinin generation and thus, prevention against HAE attacks.
	Important information about its composition Lanadelumab is a non-plasma derived recombinant, fully human monoclonal antibody (IgG1/ κ-light chain) produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology. The molecular mass of lanadelumab is 145,716.2 Da based on the amino acid sequence of the assembled IgG composed of light and heavy chains. The calculated molecular mass of the reduced light chain is 23,424 Da. The calculated molecular mass of the reduced and non-glycosylated heavy chain is 49,450 Da. The composition of lanadelumab drug product is: • *Active Ingredient:* One mL contains 150 mg of lanadelumab solution.

<table>
<tr><td></td><td>• <u>Inactive Ingredients:</u> Disodium phosphate dihydrate, Citric acid monohydrate, Histidine, Sodium chloride, Polysorbate 80 and Water for injections.
(Takhzyro Summary of Product Characteristics)</td></tr>
<tr><td>Hyperlink to the Product Information</td><td>Summary of Product Characteristics (SmPC)</td></tr>
<tr><td rowspan="2">Indication(s) in the EEA</td><td>Current:
Routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 years and older.</td></tr>
<tr><td>Proposed:
Not applicable.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
<u>Posology</u>:
Adults and Adolescents 12 to less than 18 years of age
The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction to 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.
In patients with a body weight less than 40 kg, a starting dose of 150 mg lanadelumab every 2 weeks may also be considered. In patients who are stably attack free on treatment, a dose reduction to 150 mg lanadelumab every 4 weeks may be considered.
Children 2 to less than 12 years of age
The recommended dose of lanadelumab for children 2 to less than 12 years of age is based on body weight (see table below).
Patients with a body weight of 20 to less than 40 kg who are stably attack free may continue with the same dose when reaching 12 years of age.
<u>Table 1 Recommend dose in children 2 to less than 12 years of age</u>
<table>
<tr><th>Body Weight (kg)</th><th>Recommended Starting Dose</th><th>Dose Adjustment</th></tr>
<tr><td>10 to less than 20 kg</td><td>150 mg lanadelumab every 4 weeks</td><td>A dose increase to 150 mg lanadelumab every 3 weeks may be considered in patients with insufficient control of attacks</td></tr>
<tr><td>20 to less than 40 kg</td><td>150 mg lanadelumab every 2 weeks</td><td>A dose reduction to 150 mg lanadelumab every 4 weeks may be considered in patients who are stably attack free on treatment.</td></tr>
<tr><td>More than 40 kg</td><td>300 mg lanadelumab every 2 weeks</td><td>A dose reduction to 300 mg lanadelumab every 4 weeks may be</td></tr>
</table></td></tr>
</table>

	<table><tr><td></td><td></td><td>considered in patients who are stably attack free on treatment.</td></tr></table> **Method of administration:** Lanadelumab is intended for SC administration only. Each TAKHZYRO unit (pre-filled syringe or vial) is intended for single use only. The injection should be restricted to the recommended injection sites: the abdomen, the thighs, and the upper outer arms. Rotation of the injection site is recommended. For adults and adolescents (12 to less than 18 years of age), TAKHZYRO may be self-administered or administered by a caregiver only after training on SC injection technique by a healthcare professional. For children (2 to less than 12 years of age), TAKHZYRO should only be administered by a caregiver after training on SC injection technique by a healthcare professional.
	Not applicable.
Pharmaceutical form(s) and strengths	**Current:** TAKHZYRO 150 mg solution for injection in pre-filled syringe TAKHZYRO 300 mg solution for injection in pre-filled syringe TAKHZYRO 300 mg solution for injection. The solution is colourless to slightly yellow, appearing either clear or slightly opalescent. The solution has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Source: Module 2.3.P.1, Module 2.5, Module 2.6.1, SmPC

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Hereditary angioedema	
Incidence	In published HAE registries and nationwide surveys, the estimated incidence of HAE ranged from approximately 1:10,000 to 1:50,000 people worldwide, which is about 20 to 100 HAE patients per million population
Prevalence	**Worldwide:** 1:50,000 **Europe:** Survey conducted in June-2010 among organisations representing patients with HAE in Austria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Norway, Spain, Ukraine and the United Kingdom. Outside Europe the survey also included Israel. The HAE population of 11,600 is extrapolated, based on an average prevalence of 1in 30,000[redacted]. • ***Austria:*** 1.55:100,000 [redacted] • **Czech Republic:** 1.85:100,000 [redacted] • ***Denmark:*** 1:70,922 [redacted] • **Greece:** 1.11:100,000 [redacted] • ***Italy:*** 1:64,935 [redacted] • ***Norway:*** 1:67,114 [redacted] • ***Poland:*** 0.87:100,000 [redacted] • ***Sweden:*** 1:66,225[redacted] • ***Spain:*** 1:91,743 [redacted] • ***Switzerland:*** 1.91:100,000[redacted] The prevalence numbers reported above are diagnosed prevalence estimates.
Demographics of the population in the proposed indication	**Age:** Studies suggest that 50% of HAE patients report their first symptoms by the age of seven[redacted] and over 66% report they became symptomatic by the age of 13. HAE attacks have been reported in children under age seven, however. The frequency and severity of HAE attacks may increase during puberty and adolescence. **Gender:** There are no gender disparities, although females may have more severe disease. The prevalence of HAE is equal in men and women, given autosomal dominant transmission of C1 inhibitor (C1-INH) gene mutations, though data suggest women generally have more severe clinical symptoms than men. **Ethnicity:** To date, there is no strong evidence of ethnic variation in prevalence rates, though country-specific data are heavily influenced by local healthcare issues affecting recognition and care for rare conditions. **Risk factors for HAE:** Risk factors associated with HAE and are often triggers of acute HAE attacks include: • mutation of the C1-INH gene • personal or family history • Use of ACE-Inhibitors

Hereditary angioedema	
	• menstruation and pregnancy • Use of estrogen-derived medicines, such as oral contraceptives and hormone replacement therapy • Anxiety/stress • Trauma to the oral cavity caused by dental procedures • Puberty and adolescence The triggers that lead to attacks are not well understood, but attacks tend to become more frequent and/or severe at times of physiological or psychological stress. Trauma, stress, infection and menstruation and pregnancy have been identified as possible triggers of HAE attacks [redacted]. In women, menstruation and pregnancy are reported to have a major effect on disease activity. Some female patients report a definite increase in the number of attacks during their menstrual periods, pregnancy, or while breast-feeding. Various medications, such as estrogen-containing agents and angiotensin-converting enzyme inhibitors, may also induce HAE attacks. Estrogen-derived medicines, such as oral contraceptives and hormone replacement therapy, are also associated with an increase in frequency and severity of HAE attacks and alternative, non-estrogen, birth control options [redacted]. Often used to treat high blood pressure, ACE-Inhibitors have been known to increase the frequency and severity of HAE attacks. Before attacks, many patients experience prodromal symptoms that can include tingling sensations or erythema marginatum, a nonpruritic and not raised rash. Given the propensity for children to suffer from upper respiratory tract infections, as well as experience local trauma, such triggers become especially concerning in this patient population.
Main existing treatment options	Contemporary medical management of HAE is divided between treatment of acute attacks and short- and long-term prophylaxis to reduce both the frequency and severity of subsequent flare-ups. However, several studies have suggested that home treatment can be safe and reduce the severity and duration of attacks. Acute treatment options for HAE include: • C1-inhibitor concentrate (human plasma derived): (Berinert®, Cetor®, Cinryze®) • Recombinant C1-inhibitor: (rhucin) Ruconest® • Bradykinin B2 receptor antagonist: icatibant (Firazyr®) Prophylactic treatments include: • C1-inhibitor concentrate • Androgens/Anabolic Steroids: danocrine (Danazol) • Antifibrinolytics Because HAE is a non-allergic form of angioedema, symptoms do not respond to treatments for allergic reactions, such as antihistamines, corticosteroids and epinephrine. Anabolic steroids are effective in reducing attack frequency in many patients but are associated with significant side effects. Because anabolic steroids are male hormones, their side effects can be particularly severe in female patients. In addition, these drugs cannot be given to pregnant women and children.

Hereditary angioedema	
Natural history of the indicated condition in the target population, including mortality and morbidity	C1-INH deficiency in HAE patients can result in attacks of non-pruritic swellings of the skin or mucosa. Angioedema attacks may be associated with prodromal symptoms, which commonly include fatigue, rash, and muscle aches. Swelling episodes may affect the extremities, face, gastrointestinal tract, genitourinary system, or larynx [redacted]. Attacks range in severity from mild to severe and can last up to 5 or more days; most patients suffer multiple attacks per year. With gastrointestinal involvement causing nausea, vomiting, and diarrhoea; abdominal attacks may even mimic an acute surgical emergency. Abdominal attacks are often associated with nausea, vomiting, and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery [redacted]. As reported in an international survey of HAE patients, 19% of American patients and 24% of European patients had an unnecessary surgical procedure secondary to misdiagnosis [redacted]. Laryngeal swelling can be life threatening, and these attacks primarily account for the 30-40% mortality rate described for HAE. Laryngeal oedema, which may occur in 50% of patients, can cause fatal asphyxiation due to obstruction of the upper airways, and is therefore an important clinical feature of the disease [redacted]. Approximately 50% of all HAE patients will experience a laryngeal attack in their lifetime, and there is no way to predict which patients are at risk of a laryngeal attack [redacted]. The incidence of death due to untreated laryngeal attacks is 30% to 40% and the risk of death is 3-fold greater in undiagnosed versus diagnosed patients [redacted]. Hence, HAE attacks require prompt treatment, often in an emergency room [redacted].
Important co-morbidities	There is a wide range of comorbidities and/or clinical conditions, of varying severity, that occur in the target population compared to the general population. The coexistence of these medical conditions and their related treatments may impact the risk, prognosis, overall clinical management and treatment in the target population [redacted]. These comorbidities and their impact may not have necessarily been observed in early-phase clinical trial population(s) due to study-specific exclusion criteria. However, as exposure to lanadelumab expands across different populations, certain coexisting conditions could potentially impact patient outcomes and the risk-benefit evaluation of lanadelumab. There are also a number of population-specific conditions such as childhood diseases and chronic conditions in elderly population like hypertension, cancer, depression, diabetes, infections. Population-based studies show that due to the increased incidence of chronic diseases with age, there is generally a higher prevalence of comorbidities in elderly patients[redacted]. • Chronic Obstructive Pulmonary Disease (COPD) • Hypertension • Anxiety and Depression • Allergy or Anaphylaxis The important comorbidities and complications of HAE (e.g., signs & symptoms, pathophysiology, exacerbations, disease progression, etc.) may confound evaluation of the risk/benefit profile of lanadelumab. The comorbidities selected for discussion in this RMP

Hereditary angioedema	
	were considered important based on their occurrence in the target population and the potential confounding effect it could have on the evaluation of the safety profile.

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human use:

Key Safety Findings	Relevance to Human Usage
Single and Repeat-Dose Toxicity	
Single-Dose Toxicity (R8050M-SHP643 [WIL-446029], P8051M-SHP643 [WIL-446030], P8052M-SHP643 [WIL-446054], P8053M-SHP643 [WIL-446058], P8055M-SHP643 [WIL-446050]) Single-dose SC and intravenous (IV) toxicity studies were conducted in rats and cynomolgus monkeys at doses up to and including 50 mg/kg (the highest dose tested). • Increases in activated partial thromboplastin time (APTT) in the 25 and 50 mg/kg groups (7.5% and 10.9% higher in males and females in the 50 mg/kg group, respectively) were observed in rats (R8050M-SHP643 [WIL-446029]). • Increases in APTT were also seen in the cynomolgus monkey study P8051M-SHP643 [WIL-446030]). APTT was increased 27.6% in the 50 mg/kg male group.	Lanadelumab administration in rats (single-dose and 4-week SC) and cynomolgus monkeys (single-dose) resulted in a non-adverse increase in APTT. Increased APTT is an indirect pharmacological effect of kallikrein inhibition [redacted] as pKal activity is required for the activation of the intrinsic coagulation pathway through contact system activators [redacted]. In humans, deficiency of factor XII or prekallikrein is not associated with abnormal bleeding, either spontaneous or during surgical procedures [redacted]. Despite the importance of pKal-driven fibrin formation in the APTT assay, lanadelumab does not appear to have any adverse effects on coagulation in rats, cynomolgus monkeys, or humans. Based on findings from single-dose and repeat-dose toxicity studies, lanadelumab was well-tolerated up to and including 50 mg/kg with no organs of toxicity identified. The no-observed-adverse-effect-level (NOAEL) was determined to be 50 mg/kg, the highest dose tested in both rats and monkeys. Based on exposures achieved at the NOAEL (50 mg/kg) in the 6-month study in cynomolgus monkeys, the non-clinical safety assessment of lanadelumab demonstrated human exposure margins of at least 21- and 23-fold greater than those noted at 300 mg q2wks based on maximum concentration occurring at t_{max} (C_{max}) and Area Under the Curve (AUC) comparisons.
Repeat-Dose Toxicity (R8056M-SHP643 [WIL-446031], P8057M-SHP643 [WIL-446032], P8058M-SHP643 [WIL-446033], P8059M-SHP643 [WIL-446051]) • In rats, non-adverse transient, prolonged APTT (up to 18.3%) was noted across all dose groups (sometimes statistically significant). No abnormal bleeding patterns or bleeding diathesis was observed in any animal with prolonged APTT. • In rats, non-adverse minor increases in alanine aminotransferase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) (1.4-fold, 1.1-fold and 1.5-fold, respectively) were observed in high dose males. In addition, minimal increases in liver weight and mild Kupffer cell hypertrophy were observed. Histologic examination did not identify evidence of hepatocyte damage. The severity of the liver findings was considered minimal and non-adverse. These findings were not observed in any study in cynomolgus monkeys. • In cynomolgus monkeys, lanadelumab was well-tolerated for up to 6 months following once weekly SC administration with systemic exposures that generally increased in a	

Key Safety Findings	Relevance to Human Usage
dose-proportional manner in males and females.	
Reproductive and Developmental Doxicity **Fertility and Early Embryonic Development (P8060M-SHP643 [8287146])** The potential reproductive toxicity of lanadelumab was assessed in sexually mature male (5 to 6 years old) and female (3 to 8 years old) cynomolgus monkeys. Effects on male fertility were assessed by testicular measurements, semen analysis, spermatogenesis staging, and reproductive organ evaluation. Effects on female fertility were assessed by daily vaginal swabbing and cycle length determination, and reproductive organ evaluation. • At doses of 10 or 50 mg/kg, no lanadelumab-related effects were observed on semen sample weight, total sperm count, density, percent motility, morphology, testicular measurements, or menstrual cycle length. • There were also no lanadelumab-related effects on organ weights, macroscopic, microscopic, or spermatogenesis staging findings. **Enhanced Prenatal and Postnatal Development (P8062M-SHP643 [8315672])** The enhanced pre- and postnatal development (ePPND) study evaluated the potential effects of lanadelumab on pregnancy and parturition, embryo-foetal development, survival, growth, as well as postnatal development of offspring up to 3 months in cynomolgus monkeys. • There were no lanadelumab-related difference in gestation length; prenatal loss (abortions and stillbirths); deaths; maternal or infant clinical observations, body weights, body weight change, or clinical pathology results; infant grip strength or external, morphological, neurobehavioral observations; infant skeletal development or organ weight differences; or macroscopic or microscopic observations that were attributed to lanadelumab. • Following SC administration of lanadelumab to maternal cynomolgus monkeys during the gestation phase, the mean maternal plasma-to-milk ratio indicated low excretion of lanadelumab in milk at approximately 0.2% of the maternal plasma level.	***Pregnancy*** There are limited data from the use of lanadelumab in pregnant women. Based on studies conducted in cynomolgus monkeys, there were no lanadelumab-related effects on fertility, pregnancy and parturition, embryo-foetal development as well as survival, growth, and postnatal development of offspring for up to 3 months. However, a risk to the pregnant woman or developing foetus cannot be excluded. As a precautionary measure, it is preferable to avoid the use of lanadelumab during pregnancy. ***Fertility*** Lanadelumab effect on fertility has not been evaluated in humans. In cynomolgus monkeys, lanadelumab had no effect on male and female fertility; exposures in this fertility study were approximately 20- and 22-fold greater than that noted at 300 mg q2wks based on C_{max} and AUC, respectively. In Study DX-2930-04, 8 subjects became pregnant during the study; 4 subjects discontinued due to pregnancy and 4 had treatment interruption with lanadelumab (One of 4 subject discontinue due to noncompliance). ***Lactation*** Available pharmacokinetic (PK) data in cynomolgus monkeys have shown low excretion of lanadelumab in milk at approximately 0.2% of the maternal plasma level. It is not known if lanadelumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed child cannot be excluded during this short period. Afterwards, lanadelumab could be used during breast-feeding if clinically needed.
Tissue Cross-Reactivity The potential tissue cross-reactivity of lanadelumab was evaluated using normal human	Tissue cross-reactivity can help identify on-target and potential off-target binding sites. The primary staining of lanadelumab is

Key Safety Findings	Relevance to Human Usage
tissues ex vivo. • Specific lanadelumab staining of endothelial cells and nervous tissues of the cerebellum (molecular cell layer, granular cell layer, and Purkinje cells), the cerebral cortex (small neurons and/or glial cells), the eye (outer plexiform layer of retina and/or nerve fibers in the optic disc), as well as the colon and small intestine (parasympathetic ganglion cells in Auerbach's plexus) were consistent with staining patterns reported for pKal. • Rare or sporadic staining was observed in the parathyroid and pituitary glands, urinary bladder serosa, and seminiferous tubules.	consistent with staining patterns reported for pKal on endothelial cells in human blood vessels and in the cell bodies of neurons in the hypothalamus, thalamus, spinal cord, cerebral cortex, and brainstem[redacted].
Local Tolerance Local tolerance was evaluated in single- and repeat-dose toxicity studies. • In both rats and cynomolgus monkeys, following 4 weeks or 6 months of repeated SC administration of vehicle or lanadelumab, microscopic findings of mixed inflammatory cell infiltrate and/or hemorrhage were observed at the injection site. • These findings were not seen at the recovery phase necropsy and were generally minimal to mild, considered related to the injection procedure, and not related to lanadelumab.	Local tolerance findings can be suggestive of injection site reactions in humans.
Immunogenicity • Lanadelumab was highly immunogenic in rats. Repeated once weekly SC administration of lanadelumab for 4 weeks to rats resulted in the development of anti-lanadelumab antibodies leading to a substantial decrease in exposure to lanadelumab in most animals. In the 5 mg/kg dose group, 65% of the animals were confirmed positive for anti-lanadelumab antibodies, while >90% of the animals were confirmed positive in the 25 and 50 mg/kg dose groups. • The incidence of anti-drug antibody (ADA) in cynomolgus monkeys was generally low with no apparent dose dependency. Following once weekly SC administration for up to 6 months, the incidence of induction of a sustained treatment-emergent ADA response ranged from 9.1% to 11%. • The incidence of a treatment-induced ADA response with repeated SC administration for 4 weeks to 6 months ranged from 9.1% to 14%. Most of the ADA-positive cynomolgus monkeys showed comparable	As with all therapeutic proteins, there is potential for immunogenicity. Based on the high incidence of anti-lanadelumab antibodies and the effect of these antibodies on lanadelumab exposure, the rat was not used for further toxicology studies. There was a correlation of ADAs in maternal animals and their infants, indicating placental transfer of the ADA from the maternal animal to the infant. In maternal monkeys with positive ADA, the ADA incidence for infant monkeys was 11%. Non-clinical immunogenicity incidence with a fully human monoclonal antibody may not correlate with the potential for hypersensitivity and/or lack of efficacy in humans. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying

Key Safety Findings	Relevance to Human Usage
toxicokinetic (TK) profiles to the others in their respective groups. • The overall ADA incidence for maternal and infant animals during gestation and postpartum phases was approximately 13% in the lanadelumab-administered groups, compared with approximately 6% in the vehicle control group, consistent with the incidence of positive response in the naïve serum from the ADA assay.	disease. For these reasons, comparison of the incidence of antibodies to lanadelumab in the studies with the incidence of antibodies in other studies or to other products may be misleading. Treatment with lanadelumab has been associated with development of treatment-emergent ADA in 11.9% (10/84) of subjects. All antibody titres were low. The ADA response was transient in 20% (2/10) of ADA-positive subjects. 2.4% (2/84) of lanadelumab-treated subjects tested positive for neutralising antibodies. The development of ADA including neutralising antibodies against Takhzyro did not appear to adversely affect the PK and pharmacodynamics (PD) profiles or clinical response.
Genotoxicity The battery of genotoxicity studies routinely conducted for pharmaceuticals is not applicable to biotechnology-derived pharmaceuticals and, therefore, was not conducted.	Lanadelumab, being a recombinant fully human mAb, is not expected to interact directly with DNA or other chromosomal material. Furthermore, its mechanism and site of action (i.e., targeting pKal) do not suggest a genotoxic risk.
Carcinogenicity Carcinogenicity studies were not conducted with lanadelumab, as based on a weight of evidence approach; lanadelumab has a low risk for carcinogenicity in humans. Furthermore, there were no neoplastic or preneoplastic lesions or signs of immune suppression observed in cynomolgus monkeys following 6 months of weekly SC administration of lanadelumab (P8058M-SHP643 [WIL-446033]). • Lanadelumab is highly immunogenic in rats, resulting in a marked reduction in systemic exposure; therefore, a 2-year rodent bioassay would not provide any biologically relevant data.	Based on a weight of evidence approach, it was concluded that lanadelumab has a low risk for carcinogenicity with chronic treatment in humans. The prognosis for prekallikrein-deficient patients is believed to be similar to age-comparable normal subjects and an increased carcinogenicity risk has not been observed [redacted]. In Study DX-2930-04 thus far, there has been only 1 non-rollover subject with a recurrence of a malignancy (gluteal fibrosarcoma), which was not attributed to treatment with lanadelumab. Therefore, there is no evidence for a pharmacologic or pathway-associated carcinogenicity risk for lanadelumab.
Safety Pharmacology Safety pharmacology endpoints were included in the pivotal 4-week repeat-dose toxicity SC studies conducted in rats and in the SC and IV studies in cynomolgus monkeys as well as in the chronic 6-month repeat-dose study in cynomolgus monkeys.	The aim of the safety pharmacology studies is to reveal any functional effects on the major physiological systems and allow for a mechanistically based explanation of specific organ toxicities, which should be considered carefully with respect to human use and indication(s) (ICH S6(R1), 2011). Based on data from these assessments, lanadelumab does not have adverse effects on these vital functions.
Cardiovascular (P8057M-SHP643 [WIL-446032], P8058M-SHP643 [WIL-446033], P8059M-SHP643 [WIL-446051]) Safety pharmacology endpoints to evaluate	Because the kinin-kallikrein system (KKS) can play a role in inflammation, vasodilation, coagulation, and pain [redacted], it is possible for some biologics to have indirect, CV effects;

Key Safety Findings	Relevance to Human Usage
cardiovascular (CV) systems were included in repeat-dose SC and IV studies in cynomolgus monkeys (up to 6 months). Endpoints included ECGs, heart rate (HR), waveform intervals (PR, QRS, RR, QT, and QTcB), and blood pressure. • Following once weekly SC administration for 4 weeks, ECG assessments showed a slightly reduced HR from approximately 7 through 18 hours post-dose, before reaching statistical significance at 19 to 20 and 21 to 22 hours post-dose (21.5% and 20.6% lower, respectively) and an associated prolonged RR interval initiating at approximately 7 hours post-dose, and reaching statistical significance at 19 to 20 and 21 to 22 hours post-dose (27.9% and 28.4% longer, respectively) only in males administered 50 mg/kg (the highest dose tested). • No adverse CV findings were observed in the 4-week IV or the chronic (6-month) SC repeat-dose toxicity study conducted in cynomolgus monkeys.	therefore, the potential for CV effects was evaluated using electrocardiogram (ECG) monitoring in pivotal repeat-dose toxicity studies. Based on the lack of concomitant changes in ECG wave form or conduction parameters, no associated alteration in behaviour, reduction in blood pressure and lack of observed clinical findings indicative of toxicity, the lower HR in cynomolgus monkeys following 4 weeks of administration, was not considered to be of toxicological significance. Lanadelumab is a monoclonal antibody; the ability of monoclonal antibodies to cause QT effect via indirection mechanisms is minimal. Based on totality of the clinical program with sufficient ECG assessment at time of maximal exposure, the mechanism of action for the proposed target and indication, and indicated population, lanadelumab did not prolong the QT/QTc interval (Module 2.5, Section 3.3.8; Module 2.7.2, Section 3.1.10).
Respiratory (P8057M-SHP643 [WIL-446032], P8059M-SHP643 [WIL-446051]) Safety pharmacology endpoints to evaluate effects on the respiratory system were included in the repeat-dose SC and IV studies in cynomolgus monkeys (4 weeks). Respiratory endpoints recorded included blood pressure and respiratory rates. Respiration rates were monitored by observation. • Lanadelumab, at SC or IV doses of 5, 25, or 50 mg/kg, administered once weekly for 4 weeks, had no effect on respiration rates in cynomolgus monkeys.	There were no lanadelumab-related effects on respiration rates in cynomolgus monkeys.
Central Nervous System (R8056M-SHP643 [WIL-446031]) Safety pharmacology endpoints to evaluate central nervous system (CNS) effects were included in a repeat-dose SC study in rats (4 weeks). Endpoints were evaluated by measuring multiple functional and behavioural parameters including home cage, handling, open field, handling, sensory, neuromuscular, and physiological observations. • Evaluations of clinical cage-side observations and a functional observational battery (FOB) at SC doses of 5, 25, or 50 mg/kg demonstrated that lanadelumab had no effect on CNS function in rats.	No effect on FOB, total motor activity or ambulatory motor activity noted in non-clinical species.

Key Safety Findings	Relevance to Human Usage
Drug Interactions No studies have been conducted with lanadelumab to evaluate PD or PK drug-drug interaction or interactions with non-medicinal substances in humans.	Given that lanadelumab is a high molecular weight IgG1 mAb, it is likely that it will be metabolized similarly to other endogenous antibodies, which include proteolysis by the liver and the reticulo-endothelial system, target-mediated elimination, and nonspecific endocytosis [redacted]. Because it is not a cytokine or a direct cytokine modulator, the risk of metabolism and transporter mediated pharmacokinetic drug interactions are considered low in humans. The use of analgesic, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic medications had no effect on clearance and volume of distribution of lanadelumab. For breakthrough HAE attacks, use of rescue medications such as plasma-derived and recombinant C1-INH, icatibant or ecallantide had no effects on clearance and volume of distribution of lanadelumab.
Other Non-clinical Safety Information **Pharmacokinetics** The non-clinical PK/TK of lanadelumab has been well characterised across all of the preclinical safety studies including the reproductive and developmental toxicity studies. Lanadelumab exhibited a typical PK profile as noted for other IgG1 molecules[redacted]: low clearance, low volume of distribution, and long half-lives (rats approximately 3 days on average and cynomolgus monkeys approximately 10 days on average), with an approximate SC bioavailability of 66% in cynomolgus monkeys. Maximum concentrations were reached 1 to 4 days and 2 to 4 days post-dose in rats and cynomolgus monkeys, respectively. (Module 2.4, Section 5)	The PK of lanadelumab was characterised by clinical observations and population modelling and simulation. PK properties of lanadelumab in HAE subjects showed linear dose-exposure response with doses up to 400 mg and reproducible exposure following SC administration up to 12 months. Based on the population PK model, the typical elimination half-life was 14.8 days and absorption half-life were 1.63 days; both total SC apparent plasma clearance ($CL_{/F}$; 0.598 L/day) and apparent volume of distribution ($V_{c/F}$; 12.8 L) are dependent on body weight. A population anticipated PK steady state is expected to be achieved in approximately 70 days (range: 42 to 140 days). (Module 2.7.2, Section 3.1.3)

Part II: Module SIII - Clinical trial exposure

Based on the cumulative data available as of 22-August-2023, a total of 665 unique subjects had known exposure to 1 or more doses of lanadelumab across all clinical trials including the open label extension study. Of the 665 total subjects exposed to lanadelumab, 255 subjects were healthy volunteers and 298 subjects had diagnosed Type I or Type II HAE. There are 125 unique subjects exposed to lanadelumab in the DX-2930-04 rollover extension study that includes 87 treatment-naïve subjects and 41 subjects who had previously received placebo in either the DX-2930-02 or DX-2930-03 studies and have subsequently received lanadelumab. An overview of clinical trial exposure across all lanadelumab clinical trials is provided in Table SIII. 1.

Table SIII. 1: Overview of Clinical Trial Exposure

Protocol Number/ Status	**Indication**	**Lanadelumab Dose / ROA**	**No. of Subjects Treated (N)**		
			Lanadelumab	Placebo	Rollover
DX-2930-01 COMPLETED	Healthy Subjects Age: 18-55 yrs	• 0.1 mg/kg SC • 0.3 mg/kg SC • 1.0 mg/kg SC • 3.0 mg/kg SC	24	8	N/A
DX-2930-02[a] COMPLETED	HAE Type I/II Age: ≥18 yrs	• 30 mg SC q2w • 100 mg SC q2w • 300 mg SC q2w • 400 mg SC q2w	24 (11*)	13 (8*)	19
DX-2930-03[b] COMPLETED	HAE Type I/II Age: ≥12 yrs	• 150 mg SC q4w • 300 mg SC q2w • 300 mg SC q4w	84 (76*)	41 (33*)	109
DX-2930-04[c] COMPLETED	HAE Type I/ II Age: ≥12 yrs	• 300 mg SC q2w	125	N/A	87
SHP643-101 COMPLETED	Healthy Subjects Age: 18-55 yrs	• 300 mg SC	32	N/A	N/A
SHP643-102 COMPLETED	Healthy Subjects Age: 18-55 yrs	• 300 mg SC (pre-filled syringe or auto-injector)	190	N/A	N/A
TAK-743-1003 COMPLETED	Healthy Subjects Age: 19-55 yrs	• 300 mg IV	9	3	NA
SHP643-301 COMPLETED	HAE Type I/II Age: 2 to <12 yrs	• 150 mg SC q2w • 150 mg SC q4w	21	N/A	N/A
SHP643-302[d] COMPLETED	HAE Type I/II Age: >12 yrs	• 300 mg SC q2w • 300 mg SC q4w	12	N/A	11
TAK-743-5007 COMPLETED	HAE Type I/II Age: >12 yrs	• 300 mg SC q2w	12	N/A	NA

Protocol Number/ Status	Indication	Lanadelumab Dose / ROA	No. of Subjects Treated (N)		
			Lanadelumab	Placebo	Rollover
SHP643-303[e] DOUBLE-BLIND COMPLETED	Non-histaminergic normal C1-INH angioedema Age: ≥12 yrs	• 300 mg SC q2w	50	27	73
TAK-743-3001 ONGOING	Non-histaminergic normal C1-INH angioedema Age: ≥12 yrs	• 300 mg SC q2w • 300 mg SC q4w	73	NA	NA
SHP643-304 ONGOING	HAE Type I/II Age: >12 yrs	• 300 mg SC q2w	20	NA	NA

Source: Module 5.3.3.1 DX-2930-01 CSR, Table 14.1.1; Module 5.3.3.2 DX-2930-02 CSR, Table 14.1.1; Module 5.3.5.1; Module 5.3.5.2 DX-2930-04 Interim CSR, Table 14.1.2.1; Module 5.3.5.3, ISS, Table 1.1

* Indicate the number of subjects who were subsequently treated in DX-2930-04 Study

[a] 11 treated and 8 placebo subjects rolled-over into DX-2930-04 Study

[b] 76 treated and 33 placebo subjects rolled-over into DX-2930-04 Study

[c] This total includes the 84 unique subjects NOT previously treated, 87 rollover subjects previously treated with lanadelumab and 41 subjects who previously received placebo from either DX-2930-02 or DX-2930-03 Study.

[d] 11 treated subjects rolled-over into TAK-743-5007 Study

[e] 77 subjects received either lanadelumab or placebo in this on-going double-blind study, 73 subject were rolled-over into TAK-743-3001

SIII.1 Duration of Exposure

Table SIII.2 summarizes the duration of exposure for the completed Studies DX-2930-03 and DX-2930-04 where subjects received multiple doses of lanadelumab for an extended period of time. In total, 12,958 doses of lanadelumab were administered to 220 subjects in the DX2930-03 and DX-2930-04 studies through a cut-off date of 19-December-2019 (the database lock date for the DX-2930-04 study), with an average of 58.9 doses of lanadelumab received per subject. Within the lanadelumab-treated population 96.4% of subjects (212/220) received exposure to lanadelumab for at least 6 months and 91.4% (201/220) of subjects were exposed for ≥9 months. One hundred twenty-six subjects (92.6%) in the placebo-rollover and non-rollover group received exposure to lanadelumab ≥12 months. Of the 76 lanadelumab-treated subjects from Study DX-2930-03 who rolled-over into the open-label extension, 70 (92.1%) received exposure to lanadelumab for at least 12 months on the DX-2930-04 study, while 64 of these subjects have received exposure for ≥18 months on the DX-2930-04 study.

Table SIII. 2: Cumulative Duration of Exposure Lanadelumab-treated Population*

Duration of exposure	Patients, n (%)
<1 Months	0
1 to <3 Months	5 (2.3)
3 to <6 Months	3 (1.4)
≥6 Months	212 (96.4)
≥ 9 Months	201 (91.4)
≥12 Months	196 (89.1)
≥18 Months	194 (88.2)

Duration of exposure	Patients, n (%)
Overall Subject-time (years)	**522.3**
Average Subject-time (years)	**2.37**

*Includes Studies DX-2930-03 and DX-2930-04 which were completed for the data lock point 22-August-2023.
Source: ISS Table 7.1, ISS Table 8.1.1

In the study SHP643-301 an average of 3321.4 mg of lanadelumab was received per subject. Within the lanadelumab-treated population 66.7% of subjects (14/21) received exposure to lanadelumab for >13 months and 28.6% (6/21) of subjects were exposed for 6-<=13 months and 4.8% (1/21) of subjects was exposed to 1-<3 months.

SIII.2. Age Group and Gender

The demographics of subjects in the completed studies. Demographic characteristics for subjects with HAE treated with lanadelumab or placebo across the key Phase 3 clinical studies is presented in Module 2.7.4, Table 11. Table SIII.3 includes data from the completed studies with HAE patients, DX2930-02, DX2930-03, DX2930-04; SHP643-301, SHP643-302, TAK-743-5007 and SHP643-303 and it also includes the completed studies with healthy patients DX-2930-01, SHP643-101, SHP643-102 and TAK-743-1003. Out of the 317 HAE subjects treated with lanadelumab 45 subjects were under the age of 18, 13 subjects were elderly >65 years, and the majority of the subjects were between the ages of 18-64. Within individual clinical studies (DX-2930-02 and DX-2930-03), the demographic characteristics were generally well balanced between each lanadelumab dose arm and placebo-treated subjects (Module 2.5, Section 4.2).

Table SIII. 3: Exposure by Age Group and Gender for Completed Studies(n=9)

Age Group (Years)	Healthy (N=255)		Treated – HAE (N=317)*		Placebo - HAE (N=81)*	
	Male	Female	Male	Female	Male	Female
Children (2 - <12)	0	0	9	12	0	0
Adolescents (12 – 17)	0	0	11	13	2	2
Adults (18 - <65)	**124**	**131**	**73**	**186**	**17**	**57**
18 - 44	83	60	45	98	8	34
45 - 64	41	71	28	88	9	23
Elderly (≥65)	**0**	**0**	**4**	**9**	**2**	**1**
65 - 74	0	0	4	8	2	1
75 - 84	0	0	0	1	0	0
85+	0	0	0	0	0	0
Total	**124**	**131**	**97**	**220**	**21**	**60**

Includes completed studies DX2930-01, DX2930-02, DX2930-03, DX2930-04, SHP643-101, SHP643-102, TAK-743-1003, SHP643-301, SHP643-302, TAK-743-5007 and SHP643-303 as of 22-August-2023.
*Includes the 33 placebo subjects who rolled-over into the DX-2930-04 study and the 8 placebo subjects from the DX-2930-02 study who participated in the DX-2930-04 study.

SIII.3. Dose

In completed Studies DX-2930-02, DX-2930-03, DX-2930-04, SHP643-301, SHP643-302, TAK-743-5007, and SHP643-303, 317 subjects with HAE have received a total of 14179 doses of lanadelumab (ranging from 30 to 400 mg). The majority (96.5%) of doses were 300 mg of

lanadelumab in the completed studies of DX-2930-02, DX-2930-03, DX-2930-04, SHP643-302, TAK-743-5007, and SHP643-303.

The majority (90%) of subjects exposed to lanadelumab in completed trials were in the 18 to <65 age group. There were 21 paediatric patients (<12) who received a total of 246 doses of lanadelumab, 24 adolescent subjects (≥12 to <18 years) who received a total of 1,446 doses of lanadelumab (150 or 300 mg). Thirteen geriatric subjects (≥65 years) received a total of 630 doses of lanadelumab (ranging from 150 to 400 mg).

Table SIII. 4: Exposure by Dose and Age Group for Completed Studies

DX-2930 Dose	Age Group [a] (Years)									
	<12		12-<18		18-65		>=65		Total	
	n	m	n	m	n	m	n	m	n	m
Healthy volunteers (DX-2930-01, SHP643-101, SHP643-102, and TAK-743-1003)										
0.1 mg/kg	0	0	0	0	6	6	0	0	6	6
0.3 mg/kg	0	0	0	0	6	6	0	0	6	6
1.0 mg/kg	0	0	0	0	6	6	0	0	6	6
3.0 mg/kg	0	0	0	0	6	6	0	0	6	6
300 mg/kg	0	0	0	0	231	239	0	0	231	239
Healthy volunteers overall	0	0	0	0	255	263	0	0	255	263
HAE patients (DX-2930-02, DX-2930-03, DX-2930-04, SHP643-301, SHP64-302, TAK-743-5007, and SHP643-303)										
30 mg/kg	0	0	0	0	4	8	0	0	4	8
100 mg/kg	0	0	0	0	4	8	0	0	4	8
150 mg/kg	21	246	1	7	24	165	3	21	49	439
300 mg/kg	0	0	23	1,439	251	11,638	12	605	285	13,682
400 mg/kg	0	0	0	0	10	38	1	4	11	42
HAE patients overall	21	246	24	1,446	260	11,857	13	630	317	14,179
Overall	21	246	24	1,446	515	12,120	13	630	572	14,442

n = Number of subjects, m = Number of doses
[a] Age group is based on age at first exposure. Data cut 22-August-2023.

In Table SIII.5 the exposure for healthy and HAE patients by race is presented. The majority of subjects exposed to lanadelumab are White (471/572).

Table SIII. 5: Exposure by Race and Gender for Completed Studies (Includes Healthy and HAE Patients)

Ethnic origin	Male	Female	Total Number of Subjects
Asian	10	24	**34**
Black or African American	30	33	**63**

[redacted]

Ethnic origin	Male	Female	Total Number of Subjects
Caucasian	179	292	**471**
Multiple	1	2	**3**
Other	1	0	**1**
Total unique patients	**221**	**351**	**572**

*Data from completed clinical trials SHP643-101, SHP643-102, DX2930-01, DX2930-02, DX2930-03, DX2930-04, TAK-743-1003, SHP643-301, SHP643-302, TAK-743-5007, and SHP643-303 as of 22-August-2023.

[redacted]

Part II: Module SIV - Populations not studied in clinical trials

During the clinical development of lanadelumab, certain sub-populations within the expected target populations may not be studied or studied to a limited degree in clinical trials due to the potential for variability in drug response and interactions which can lead to the possibility of adverse reactions and/or difficulties in the interpretation of PKs, PDs and clinical safety results in trial subjects that can impede the full evaluation of the safety profile of lanadelumab.

The exclusion of these sub-populations of subjects may limit the ability to detect or predict ADRs which may result from a combination of factors related to drug-related effects, underlying disease state, comorbid conditions, and concomitant medications. Subjects are excluded from lanadelumab clinical trials based on the following factors:

- Mechanism of action of lanadelumab based on the known biology of the plasma kallikrein-kinin pathway and its roles in HAE pathogenesis
- Based on clinical experience with other similar molecules indicated for the treatment of HAE

Based on the objectives for each clinical study, the following populations may have not been studied or studied to a limited degree during the clinical development of lanadelumab:

- Pregnant or Lactating Women
- Patients taking concomitant ACE-inhibitors
- Patients with abnormal liver function tests (ALT or AST >3x Upper limit of normal (ULN) or total Bilirubin >2x ULN)
- Patients on long-term or short-term prophylactic therapy for HAE (C1-INH, attenuated androgens or antifibrinolytics)

Concomitant diagnosis of another form of chronic, recurrent angioedema (e.g., AAE, Type III HAE, idiopathic angioedema, or recurrent angioedema associated with urticarial).

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

Pregnant or lactating women	
Reason for exclusion:	The safety of lanadelumab for use during pregnancy or in nursing mothers is not known.
Is it considered to be included as missing information?:	Yes
Rationale:	Non-clinical studies conducted in cynomolgus monkeys, demonstrated there were no lanadelumab-related effects on fertility, pregnancy and parturition, embryo-foetal development as well as survival, growth, and postnatal development of offspring for up to 3 months. Available pharmacokinetic data in cynomolgus monkeys have shown low excretion of lanadelumab in milk at approximately 0.2% of the maternal plasma level.

Patients taking concomitant ACE-inhibitors	
Reason for exclusion:	Decreasing activity of these peptidases (such as by using an ACE inhibitor) can increase the

Patients taking concomitant ACE-inhibitors	
	half-life of bradykinin and potentially worsen HAE disease severity
Is it considered to be included as missing information?:	No
Rationale:	Not applicable

Patients taking any estrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy)	
Reason for exclusion:	Hormones, specifically oestrogen containing medications can trigger angioedema attacks
Is it considered to be included as missing information?:	No
Rationale:	Not applicable

Patients with abnormal liver function tests (ALT or AST >3x ULN or total bilirubin >2x ULN)	
Reason for exclusion:	These criteria were based on some non-severe liver effects in one rat study. As a precaution, this patient population was excluded from clinical trials.
Is it considered to be included as missing information?:	No
Rationale:	There are no specific safety concerns in this population. Liver-related biochemistry abnormalities were observed at baseline in ~14% of subjects.

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/cumulative exposure.

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	There were eight subjects exposed. The average childbearing age, as defined by World Health Organisation (WHO), is from 18 – 44 years. Approximately 47% of our lanadelumab-treated patients were women of childbearing age.
Breast-feeding women	

Type of special population	Exposure
	All subjects discontinued treatment with lanadelumab upon receipt of positive serum/urine pregnancy test. An ePPND study in cynomolgus monkeys does not indicate effects of lanadelumab on embryo-foetal development. Lanadelumab has not been studied in lactating females. It is not known whether lanadelumab is present in human milk. Available pharmacokinetic data in cynomolgus monkeys has shown excretion of lanadelumab in the milk of lactating monkeys at approximately 0.2% of the maternal serum level in an ePPND study.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	• Patients with hepatic impairment Lanadelumab has not been studied in subjects with hepatic impairment or renal impairment Baseline hepatic biomarkers of ALT, AST, and/or bilirubin had no effect on PK of lanadelumab. • Patients with renal impairment Renal impairment estimated glomerular filtration rate (eGFR): 60 to 89 mL/min/1.73 m^2 [mild, n=98] and 30 to 59 mL/min/1.73 m^2 [moderate, n=9]) had no effect on $C_{L/F}$ and $V_{c/F}$ of lanadelumab, suggesting the elimination of lanadelumab is possibly due to the IgG class acting via nonspecific clearance through cells of the reticuloendothelial system ([32]; Module 2.5, Section 3.3.9; Module 2.7.2, Figure 20). • Patients with cardiovascular impairment Not applicable. • Immunocompromised patients Not applicable. • Patients with a disease severity different from inclusion criteria in clinical trials Not applicable.
Population with relevant different ethnic origin	White Caucasian (93.2%) with 11 (5.0%) black subjects, 2 Asian (0.9%). Use in particular patient populations within the approved indication, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far Hereditary angioedema (HAE) is an autosomal dominant disease due to mutations in the C1-INH gene that affects protein synthesis (HAE type I) or function (HAE type II). The study population of in lanadelumab trials was predominantly from the USA and white Caucasian (93.2%) with 11 (5.0%) black subjects, 2 Asian (0.9%). As elucidating any safety concerns associated with any genetic/ethnic variances could not be determined. This should be acceptable if arguments are presented that there are no important differences that could affect interpretation of results i.e., genetics, or differences in patient care from region to region. Pharmacokinetic parameter Use in particular patient populations within the approved indication, for which there is insufficient medicinal product exposure to determine whether the safety profile differs from that characterised so far Hereditary angioedema (HAE) is an autosomal dominant disease due to mutations in the C1-INH gene that affects protein synthesis (HAE type I) or function (HAE type II).

Type of special population	Exposure
Sub-populations carrying relevant genetic polymorphisms	Not applicable.
Other	
Paediatric patients	45 subjects exposed. The study SHP643-301 is completed in paediatric patients aged 2-11 years of age. Paediatric development of Lanadelumab has been limited to children and adolescents (ages 2 to 17 years). It was not developed for paediatric population below the age of 2 years because in pre-term newborns, neonates (birth to 27 days) and in infants and toddlers (28 days to 23 months) as the condition does not typically manifest, or is not diagnosed until a later age, in these subsets. There were no developmental concerns based on pharmacological class. In subjects with HAE, no influence of age was apparent on $C_{L/F}$ of lanadelumab after correcting for body weight. Based on estimated mean post hoc PK parameters, an ~37% higher exposure ($AUC_{tau,ss}$) in adolescents (aged 12 to 17 years) than adults (aged 18 to 65 years) was demonstrated, as expected. Based on the PK, efficacy, and safety, no dosing regimen adjustment is recommended for adolescent patients (Module 2.5, Section 3.3.9; Module 2.7.2).
Geriatric patients	13 Subjects exposed. Pharmacokinetic results suggest no difference in the PK properties and exposure of lanadelumab between elderly (>65 years) and adult subjects (18 to 65 years), supporting that no dose adjustment is required for elderly subjects with HAE (>65 years) (Module 2.5, Section 3.3.9; Module 2.7.2, Table 14).

[redacted]

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

Formula for 300 mg:

For lanadelumab, the methodology used to calculate the exposure assumes that each patient receives 1 dose (300 mg) every 2 weeks or 26 doses per year (the number of doses over the course of a full year). Each dose distributed consisted of 1 vial containing 300 mg of lanadelumab.

Estimated patient year exposure = (number of vials/ pre-filled syringe [PFS] distributed)/(26 doses/year [assuming 1 dose every 2 weeks])

Formula for 150 mg:

For lanadelumab, the methodology used to calculate the exposure assumes that each patient receives 1 dose (150 mg) every 3 weeks or 17 doses per year (the number of doses over the course of a full year). Each dose distributed consisted of 1 vial containing 150 mg of lanadelumab.

Estimated patient year exposure = (number of vials/PFS distributed)/(17 doses/year [assuming 1 dose every 3 weeks])

SV.1.2. Exposure

Exposure for 300 mg:

Based on the methodology, the patient exposure can be estimated to be 296,697 vials/PFS corresponding to 11,413 PYs of treatment cumulatively.

[redacted]

Exposure for 150 mg:

Based on the methodology, the patient exposure can be estimated to be 406 Vials/PFS, corresponding to 24 PYs of treatment cumulatively.

[redacted]

[redacted]

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Lanadelumab has no known potential for abuse or dependence based on the pharmacological characteristics and non-clinical data.

Part II: Module SVII - Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason 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):

Safety concern	Justification for NOT including in RMP
Dizziness	Dizziness is an adverse reaction listed in section 4.8 of the SmPC, but it is not associated to a relevant risk.
Myalgia	Myalgia is an adverse reaction listed in section 4.8 of the SmPC, but it is not associated to a relevant risk.
Rash maculo-papular	Listed in section 4.8 of the SmPC, however only was reported in 2 of 212 lanadelumab-treated subjects (0.9%). This event can be a sign/symptom of HAE or hypersensitivity. The clinical impact of this risks on patients is considered minimal in relation to the severity of the indication treated and these risks should therefore not be classified as important.
Medication errors	There are no potentially important safety concerns with regards to medication errors; lanadelumab is intended for self-administration or administration by a caregiver, therefore the patient or caregiver should be trained by a healthcare professional. Subjects in Study DX-2930-04 were allowed to initiate self-administration after receiving the required training and receiving the first 2 doses of lanadelumab at the study site. There was no impact of self-administration on the prevention of attacks provided by lanadelumab. To evaluate the safety of self-administering lanadelumab, TEAEs (excluding HAE attack reported AEs) were assessed by the most recent administration type; "self-administration at home", "self-administration in clinic", or "study staff in clinic". Overall, the event rate for TEAEs with self-administration was low, appeared to be well-tolerated, and was comparable to rate of TEAEs with study staff administrations. A low event rate for SAEs, severe TEAEs, and discontinuations due to a TEAE was observed across all administration type categories. In addition, detailed instructions are provided with pictures in the patient medication information. In addition, patients are to be trained by a healthcare professional on proper administration technique. There will be on-going monitoring for any important impacts of these types of events on the risk-benefit profile.
Overdose	There are no potentially important safety concerns with regards to overdose; the potential for harm from either intentional or accidental overdose is minimal based on PK data from non-clinical and clinical studies. The non-clinical safety assessment of lanadelumab demonstrated a human exposure margin for the 300 mg q2wks regimen in study DX-2930-03 of at least 21 and 23-fold, based on C_{max} and AUC comparisons, respectively following chronic (6-month) administration in monkeys. In clinical trials, there have been no reports of overdose or major

Safety concern	Justification for NOT including in RMP
	dose-related toxicities with lanadelumab. In Study DX-2930-02, HAE subjects received doses up to 400mg SC lanadelumab. The highest dose administered during clinical trials for the long-term prophylaxis to prevent angioedema attacks was 300 mg q2wks, which 29 subjects received for at least 1 year with no evidence of dose-limiting toxicity (Module 2.7.4). There will be on-going monitoring for any important impacts of these types of events on the risk-benefit profile.
Off-label use	There is a potential for off-label use in other types of angioedema including bradykinin-mediated angioedemas, acquired AE, idiopathic. However, there are no data on off-label use. There will be on-going monitoring for any important impacts of these types of events on the risk-benefit profile.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Not applicable.

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 to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Safety concern	Justification for NOT including in RMP
Injection site reaction	All reported injection site reactions were non-serious, and mild to moderate in severity. These reactions may be related to SC route of administration as well.

Known risks that do not impact the risk-benefit profile

Not applicable.

Other reasons for considering the risks not important

Not applicable.

There are no potentially important safety concerns with regards to medication errors, overdose and or off-label use; however, there will be on-going monitoring for any important impacts of these types of events on the risk-benefit profile.

There have been no observed PK and PD interactions with Lanadelumab. Concomitant medications (used by the subject while on treatment for ≥20% of treatment duration) such as analgesic, antibacterial, antihistamine, anti-inflammatory, antirheumatic, and rescue medications used in the treatment of HAE had no effect on $CL_{/F}$ and $V_{c/F}$ of lanadelumab. In addition, routine treatment with lanadelumab is associated with reduction in concomitant use of analgesic or anti-inflammatory/anti-rheumatic drugs and rescue medications including C1-INH, icatibant, and ecallantide. This finding shows that lanadelumab is associated with reduction in pain, inflammation, or nonspecific discomfort associated with significant reduction in number of HAE attacks. (Module 2.5, Section 3.3.6).

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
Hypersensitivity	As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events were considered adverse

Important Identified Risks	Risk-benefit impact
	event of special interest (AESI) for Study DX-2930-03 and Study DX-2930-04. Hypersensitivity may lead to a serious outcome including anaphylaxis, and/or discontinuation of the treatment if not managed appropriately, even if the adverse reaction is not serious.

Important Potential Risks	Risk-benefit impact
Immunogenicity	Repeated administration of lanadelumab may lead to immunogenicity and formation of ADA. ADA may potentially lead to the reduction of efficacy or safety events.

Important Potential Risks	Risk-benefit impact
Liver Toxicity	Administration of lanadelumab may lead to elevated transaminase levels. Clinically significant elevations (>3X ULN) occurred in the same percentage (4.8%) of subjects whether exposed to placebo or lanadelumab. Elevated bilirubin level in hepatocellular-type (TA > 3X ULN), drug-induced liver injury (DILI) is a reflection of the severity of injury, cell death, and hepatocellular dysfunction. This rule (Hy's law) has historically been used to judge the severity of DILI in clinical trials [redacted]. In lanadelumab clinical trials, TA elevations were not associated with elevated bilirubin levels and there were no Hy's law cases or acute liver failure. The risk-benefit balance remains positive in the overall HAE population.

Missing Information	Risk-benefit impact
Long-term safety in paediatric population	There are no specific safety concerns in children, as compared to the adult population. However, long-term safety data have not been studied in the paediatric population. In such case, 'long-term safety in children' is considered to be missing information.
Long-term safety in adult population	Data on long-term safety in adult population beyond two years of lanadelumab exposure is relatively limited. In such case, 'long-term safety in adults' is considered to be missing information.
Use in Pregnancy and Lactation	There are no specific safety concerns in pregnant and lactating women. However, there is limited data from the use of lanadelumab in pregnant women and is unknown whether lanadelumab is excreted in human milk. In such case, 'Use in Pregnancy and Lactation' is considered to be missing information.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

None.

SVII.3.2. Presentation of the missing information

Missing information: Use in Pregnancy and Lactation	
Evidence source:	Not applicable
Population in need of further characterisation	Use in Pregnancy and Lactation

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in Pregnancy and Lactation

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

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.

Specific adverse reaction follow-up questionnaires for Safety Concerns

Not applicable.

Other forms of routine pharmacovigilance activities for Safety Concerns

Not applicable.

III.2. Additional pharmacovigilance activities

None.

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Use in Pregnancy and Lactation	**Routine risk communication:** SmPC section 4.6 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None.

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.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in Pregnancy and Lactation	**Routine risk minimisation measures:** SmPC section 4.6 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

Part VI: Summary of the risk management plan

Summary of risk management plan for Takhzyro® (Lanadelumab)

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

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

This summary of the RMP for Takhzyro 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 Takhzyro's RMP.

I. The medicine and what it is used for

Takhzyro is authorised for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 years and older (see SmPC for the full indication). It contains lanadelumab as the active substance and it is given by subcutaneous route.

Further information about the evaluation of Takhzyro's benefits can be found in Takhzyro's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/takhzyro.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Takhzyro, together with measures to minimise such risks and the proposed studies for learning more about Takhzyro'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 Periodic Safety Update Report (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 Takhzyro is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Takhzyro 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 Takhzyro. 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);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in Pregnancy and Lactation

II.B Summary of important risks

Missing Information: Use in Pregnancy and Lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

II.C. Post-authorisation development plan

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 lanadelumab.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for lanadelumab.

[redacted]

Part VII: Annexes

Table of contents

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

[redacted]

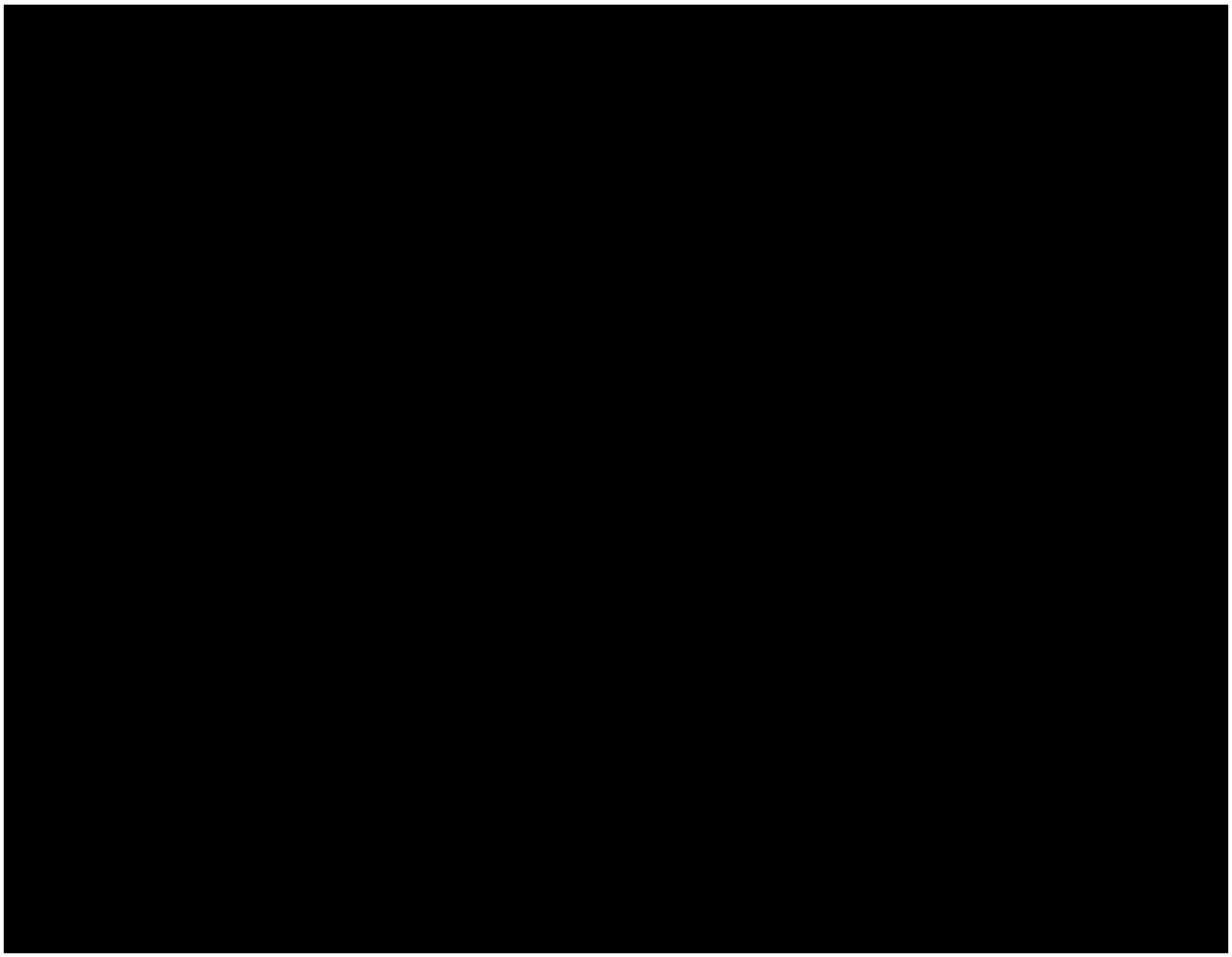
Annex 6: Details of proposed additional risk minimisation activities (if applicable)

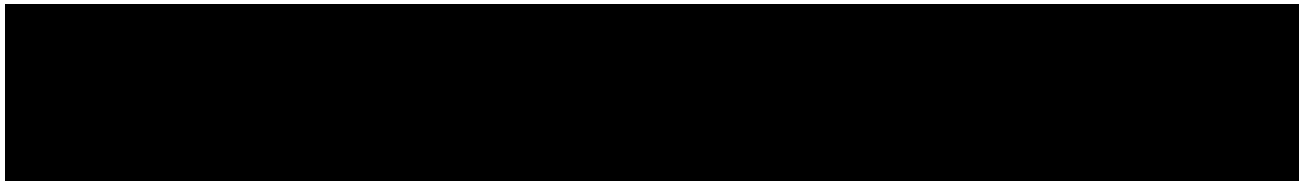
[redacted]

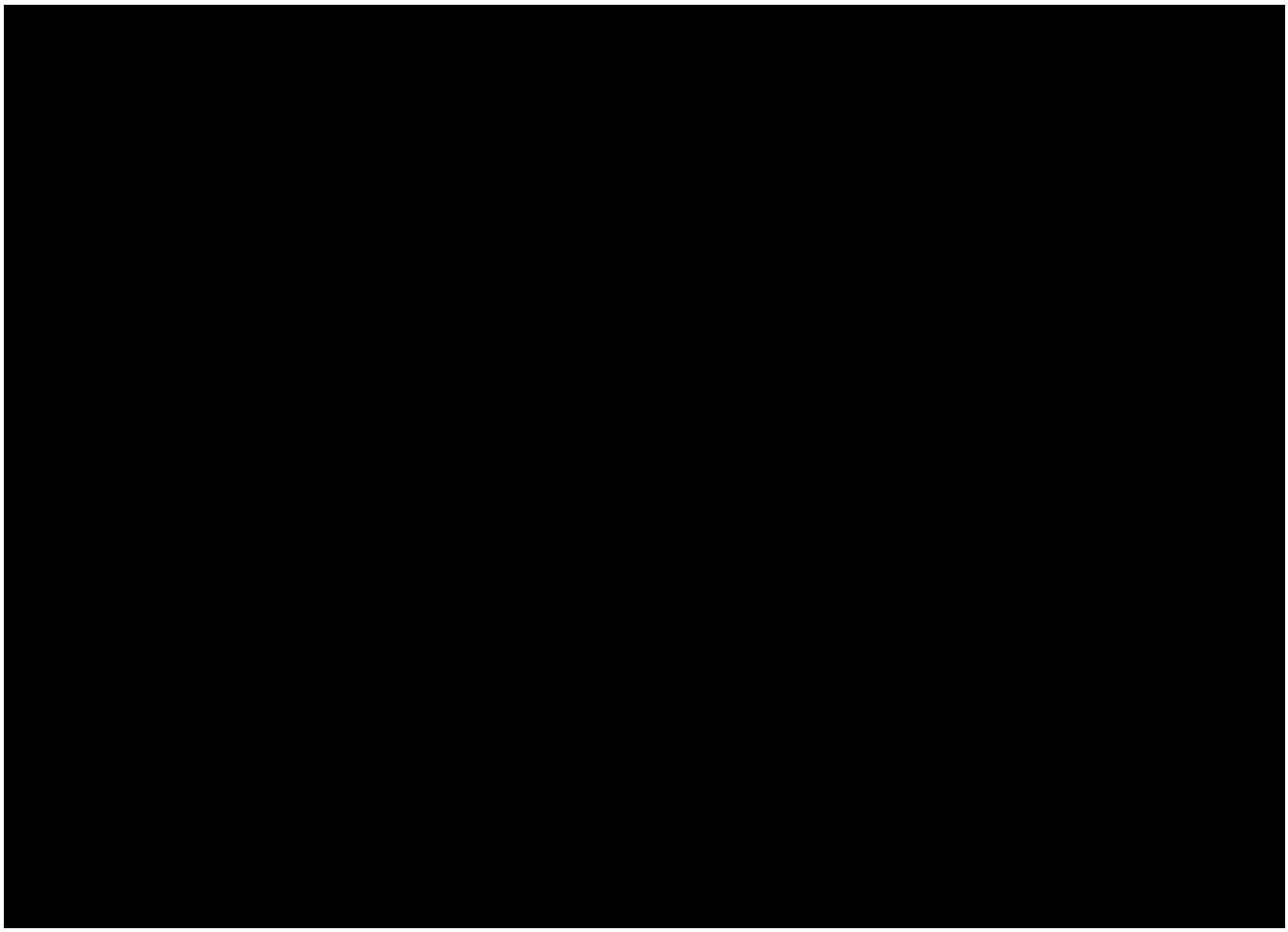
[redacted]

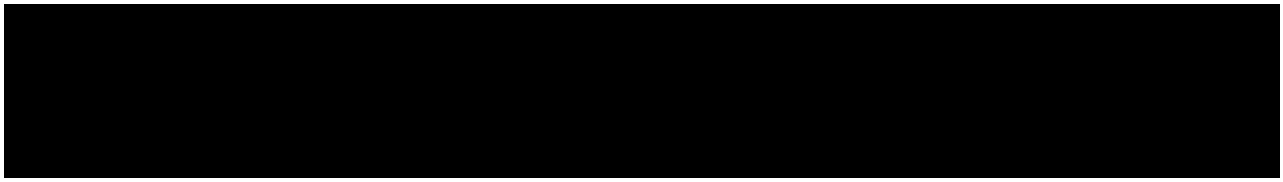
[redacted]

[redacted]



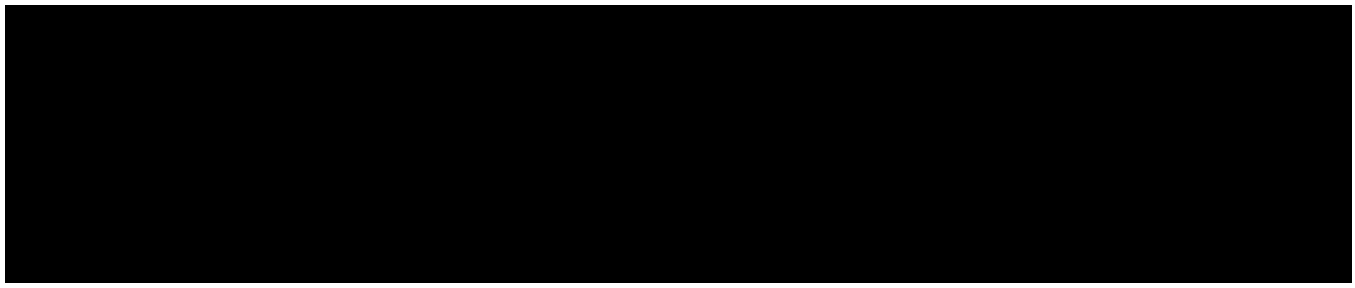


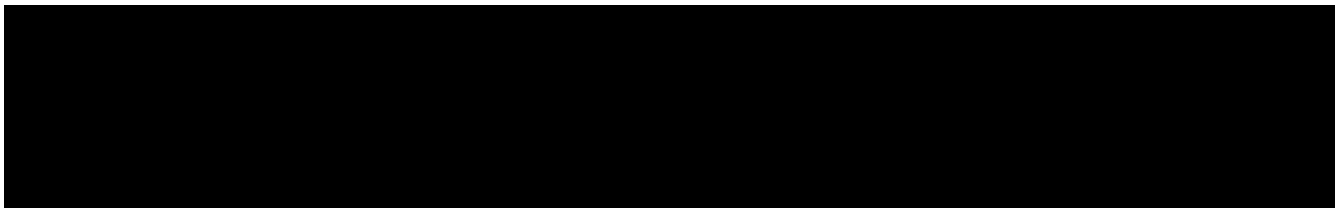




Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.





[redacted]

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

[redacted]