18 October 2018
EMA/794314/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TAKHZYRO

International non-proprietary name: lanadelumab

Procedure No. EMEA/H/C/004806/0000

Note

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

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List of abbreviations

ADA	anti-drug antibody
ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse events
AE-QoL	Angioedema Quality of Life
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AUC	area under the plasma concentration-time curve
BLQ	below the limit of quantification
BMI	body mass index
C1-INH	C1-esterase inhibitor
CDC	complement dependent cytotoxicity
CDR	complementarity determining regions
CFU	*colony-forming unit*
cGMP	current good manufacturing practices
CI	confidence interval
cHMWK	Cleaved High Molecular Weight Kininogen
CHO	Chinese hamster ovary
CL/F	apparent total plasma clearance after extravascular administration
CPP	critical process parameter
CPV	continued process verification
CQA	critical quality attribute
CSR	Clinical study report
DNA	deoxyribonucleic acid
DOE	design of experiments
DP	drug product
DS	drug substance
DSC	differential scanning calorimetry
eCRF	electronic case report form
EAUC50	effective area under concentration curve associated with 50% of the maximum effect
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5-dimension 5-level
E-R	exposure-response
Fc	fragment crystallisable
FWER	Family-wise type I error rate
GEE	Generalized estimating equations
GLM	Generalized linear model
GMP	good manufacturing practice
HAARP	HAE attack assessment and reporting procedures
HAE	hereditary angioedema
HC	heavy chain

HCP	host cell protein
HDPE	high density polyethylene
HMW	high molecular weight
HMWK	high molecular weight kininogen
HPLC	high-performance liquid chromatography
HRQoL	health related quality of life
HMWK	high molecular weight kininogen
ICH	International Conference on Harmonisation
IC50	effective lanadelumab concentrations associated with a 50% reduction in cHMWK activity
Ig	immunoglobulin
IMP	Investigational medicinal product
IP	Investigational product
IPC	in-process control
ISS	Integrated summary of safety
ITT	Intent-to-treat
Kd	dissociation constant
KM	Kaplan-Meier
LC	light chain
LMW	low molecular weight
LS	Least squares
LTP	Long-term prophylaxis
MCB	master cell bank
MCID	minimal clinically important difference
MI	Multiple Imputation
MMRM	Mixed model repeated measures
MMV	mouse minute virus
N/A	not applicable
NF	National Formulary
NOR	normal operating ranges
OLE	Open-label extension
OR	odds ratio
PAR	proven acceptable ranges
PD	Pharmacodynamic(s)
Ph Eur	European Pharmacopoeia
PK	Pharmacokinetic(s)
pKal	plasma kallikrein
PPQ	process performance qualification
PRO	patient reported outcome
PRV	Pseudo Rabies Virus
QoL	Quality of life
q2wks	every 2 weeks
q4wks	every 4 weeks
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDS	sodium dodecyl sulfate

SDS-cGE	sodium dodecyl sulfate capillary gel electrophoresis
SE-HPLC	size exclusion high performance liquid chromatography
SmPC	Summary of Product Characteristics
SPR	surface plasmon resonance
TI	tolerance interval
TSE	transmissible spongiform encephalopathy
UF/DF	ultrafiltration/diafiltration
US	United States
USP	United States Pharmacopeia
VAS	Visual analogue scale
VcF	apparent volume of distribution
WCB	working cell bank
WHO	world Health Organization
xMuLV	Xenotropic murine leukemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shire Pharmaceuticals Ireland Limited submitted on 12 March 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for TAKHZYRO, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 April 2017.

TAKHZYRO, was designated as an orphan medicinal product EU/3/15/1551 on 9 October 2015 in the following condition: Treatment of hereditary angioedema.

The applicant applied for the following indication:

TAKHZYRO is indicated for routine prevention of angioedema attacks and the control of symptoms of hereditary angioedema (HAE) in patients aged 12 years and older.

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0273/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0273/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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

https://www.ema.europa.eu/en/medicines/human/EPAR/takhzyro.

Similarity

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

Applicant's request(s) for consideration

Accelerated assessment

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

New active Substance status

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

Protocol assistance

The applicant did not seek Protocol assistance at the CHMP.

1.2. Steps taken for the re-examination procedure

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

Rapporteur: Kristina Dunder Co-Rapporteur: Joseph Emmerich

The application was received by the EMA on	12 March 2018
Accelerated Assessment procedure was agreed-upon by CHMP on	22 February 2018
The procedure started on	29 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	29 May 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	29 May 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	5 June 2018
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 June 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 June 2018
The applicant submitted the responses to the CHMP consolidated List of	16 August 2018

Questions on	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	06 September 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	18 September 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 September 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	04 October 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to TAKHZYRO on	18 October 2018
The CHMP adopted a report on similarity of TAKHZYRO product with name of the authorised orphan medicinal product(s) on	18 October 2018

2. Scientific discussion

2.1. Problem statement

The claimed indication for lanadelumab is for routine prevention of angioedema attacks and the control of symptoms of hereditary angioedema (HAE) in patients aged 12 years and older.

2.1.1. Epidemiology

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by unpredictable recurrent episodes of subcutaneous or submucosal oedema typically affecting the skin, upper airway, and gastrointestinal tract.

At the time of the orphan designation (procedure number EMA/COMP/603277/2015 dated 13 November 2015), hereditary angioedema affected less than 0.5 in 10,000 people in the European Union (EU).

2.1.2. Aetiology and pathogenesis

Hereditary angioedema is caused by mutations in the gene coding for C1 esterase inhibitor (C1-INH), resulting in deficiency (HAE type I) or dysfunction (HAE type II) of C1-INH protein.

C1-INH is the major serine protease inhibitor of the early complement proteases as well as the contact system proteases, plasma kallikrein and coagulation factor XIIa. Deficiency of C1-INH within the kallikrein-kinin (contact system) is believed to result in the loss of inhibition of plasma kallikrein activity leading to the increased bradykinin release from high-molecular-weight kininogen (HMWK) and vascular leak mediated by bradykinin binding to the B2 receptor (B2-R) on the surface of endothelial cells.

2.1.3. Clinical presentation, diagnosis

Acute angioedema attacks in HAE are characterized by painful, non-pruritic swelling of the face, larynx, gastrointestinal (GI) tract, limbs, and/or genitalia, which may last up to 5 or more days. Most patients suffer multiple attacks per year and most patients with HAE experience attacks at multiple sites. Abdominal attacks are often associated with nausea, vomiting, and severe pain; intestinal symptoms resembling abdominal emergencies may lead to unnecessary surgery (Zuraw, 2008).

Approximately 50% of all patients with HAE will experience a potentially life-threatening laryngeal attack in their lifetime (Bork et al., 2006). The incidence of death due to untreated laryngeal attacks is 30% to 40% and the risk of death is 3-fold greater in undiagnosed vs diagnosed patients (Bork et al., 2012; Bork et al., 2000). An audit conducted in the United Kingdom identified 55 HAE-related deaths in 33 families (Jolles et al., 2014). One death secondary to laryngeal oedema was recorded among 10 HAE patients included in a recent French study (Javaud et al., 2015).

Due to the unforeseeable nature of the attacks, HAE has an important negative impact on the quality of life for patients suffering from the disorder. Among other things, frequent attacks negatively affect education and work. Since symptoms often begin by age of 10, this is especially important in children and adolescents as negative effects on performance in school will affect the future professional career.

Three types of HAE have been described:

- HAE type 1 is caused by deletion or by expression of a truncated transcript leading to a quantitative defect in C1-INH;
- HAE type 2 is caused by point mutations leading to a qualitative defect in C1-INH.
- HAE type 3 predominantly involves females, with the use of oestrogen-containing oral contraceptives and pregnancy being precipitating factors. HAE type 3 is not caused by C1-INH deficiency but is associated with an increase in kininogenase activity leading to elevated levels of bradykinin.

2.1.4. Management

Several clinically effective options for treating and preventing HAE attacks are approved for use. These include agents targeted at different components of the kallikrein-kinin pathway. C1-INH replacement therapy is achieved with human plasma-derived C1-INH (pdC1-INH) concentrates or recombinant human C1-INH. Ecallantide inhibits kallikrein activity and icatibant acts as bradykinin B2 receptor antagonist.

HAE International treatment guidelines state that the goal of prophylactic treatment is to reduce the frequency and severity of attacks and thus to increase patients' quality of life. The treatment guidelines recommend C1-INH or attenuated androgens as standard of care to prevent HAE attacks however, there are numerous contraindications, therapeutic class adverse events (AEs), risk factors for AEs, tolerance to therapy, and overall suboptimal control of HAE due to the need higher or more frequent dosing, threat of breakthrough attacks, and low attack-free rates.

Plasma-derived C1-INH for intravenous use is approved European Union (EU)-wide for routine prevention of HAE attacks in adults, adolescents and children (6 years old and above) with severe and recurrent attacks, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment. It requires IV infusion every three or four days due to its short half-life and may necessitate the placement of an indwelling catheter. Plasma-derived C1-INH has class warnings

including hypersensitivity, thromboembolic events, and viral safety (risk of transmission of infectious agents) due to its plasma derivation.

Berinert, a plasma-derived C1-INH for subcutaneous injection twice weekly, was recently approved for the prevention of HAE in EU through the decentralised procedure. The procedure involved 22 member states, thus the treatment will not be available in all member states.

In addition, while not indicated for HAE patients in all EU countries, attenuated androgens and antifibrinolytics are available in many countries and used for prophylaxis in HAE patients.

Current treatment guidelines recommend against the use of antifibrinolytics for long-term prophylaxis (LTP) due to limited efficacy. Attenuated androgens (e.g. danazol, stanozolol, and oxandrolone) increase hepatic production of C1 INH protein and are limited by safety issues.

In spite of available medicinal products for the treatment of acute attacks, HAE still is a disorder with high mortality. Although existing preventive therapy with C1-INH ameliorates the number and severity of attacks, some patients still experience breakthrough attacks.

About the product

Lanadelumab is a recombinant fully human IgG1 monoclonal antibody inhibitor of active pKal that binds both soluble and membrane-bound forms of the enzyme. It is hypothesized that by specifically inhibiting pKal, lanadelumab will prevent the release of bradykinin from HMWK, thereby preventing the vascular leak and swelling that is initiated when bradykinin binds to the B2 receptor.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. In spite of available medicinal products for the treatment of acute attacks as well as prevention of attacks, HAE remains a disorder with high mortality with some patients still experiencing life threatening breakthrough attacks.

The administration via subcutaneous route and frequency of administration of lanadelumab (Q2 weeks) offers an improvement for patient care compared to other substances registered for prevention of HAE attacks in the EU.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a sterile preservative-free solution for subcutaneous administration containing 300 mg of lanadelumab as the active substance at a concentration of 150 mg/ml. Each 300 mg vial is filled with a nominal volume of 2.0 ml of finished product.

Other ingredients are: disodium phosphate dihydrate, citric acid monohydrate, histidine, sodium chloride, polysorbate 80 and water for injections (WFI).
The finished product primary packaging components consist of a Type I glass vial, a rubber stopper, and a crimp seal with cap. Two needles and one syringe are provided together in an administration kit that will be co-packaged with the lanadelumab finished product vial. The medical devices (needle and syringe) are CE marked.

2.2.2. Active Substance

General Information

Lanadelumab (INN) is a recombinant fully human IgG1 kappa light chain monoclonal antibody expressed in Chinese Hamster Ovary (CHO) cells, discovered by screening an antibody phage display library against active plasma kallikrein. Lanadelumab is composed of two light (213 residues) and two heavy (451 residues) chains (MW 145.7 kDa, theoretical, non-glycosylated). The identified affinity matured antibody was codon optimized for expression in Chinese hamster ovary (CHO) cells. Lanadelumab contains six unique (4 H-H and 2 L-L) intra-chain and three (2 H-H and 1 H-L) unique inter-chain disulfide bonds.

Complementarity determining regions (CDRs) in lanadelumab bind plasma kallikrein to occlude the active site and inhibit proteolysis of the endogenous substrate, high molecular weight kininogen (HMWK), thereby attenuating the generation of bradykinin, the potent vasodilator and mediator of hereditary angioedema pathology. The applicant concludes that lanadelumab have minimal Fc effector function potential.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Lanadelumab active substance is manufactured by Rentschler Biopharma SE, Laupheim, Germany (Rentschler). All sites involved in lanadelumab active substance manufacturing and testing are GMP compliant.

A batch of active substance is defined as the material purified from one single-use production bioreactor, cultivated from a single working cell bank (WCB) vial. The entire content of the bioreactor is purified to produce lanadelumab active substance.

The active substance is produced using mammalian derived cells. The lanadelumab cell culture process includes vial thaw (one single WCB vial), inoculum expansion through a series of vessels with increasing working volumes (shake flasks, rocking and stirred tank bioreactors), a fed-batch production bioreactor, and cell culture harvest clarification utilizing depth and 0.2 µm filtration. Immediately prior to harvest, samples are withdrawn for tests of adventitious agents. At harvest the production bioreactor is cooled and the entire content is filtered.

The lanadelumab purification process includes chromatography steps, viral inactivation and filtration steps and two ultrafiltration/diafiltration (UF/DF) steps for concentration and buffer exchange. The filtration and filling step includes conditioning of the process stream, filling of the active substance into bottles and freezing.

Multiple cycles of each purification unit operation are employed to process an entire harvest.

Reprocessing (defined as a one-time 0.2 µm refiltration) is acceptable for the chromatography step pools. There is no impact on product quality after refiltration in these steps.

Refiltration will be concurrently validated.

A product and process control strategy in accordance with ICH Q8, Q9 and Q10 guidance has been established. Elements of the control strategy are defined as follows:

- Critical quality attributes (CQAs) are the properties or characteristics for which an acceptable range has been established to ensure the desired product quality.

- Process parameters are input variables that can be directly controlled, and critical process parameters (CPP) are those whose variability has an impact on a CQA. All input variables that do not have an impact on a CQA are designated as non-CPPs.
- Performance attributes (PA) are output variables or outcomes that cannot be directly controlled but indicate that the process performed as expected. An in-process control (IPC) is a performance attribute that may be an indicator of product quality.

The acceptable ranges of the CPPs are considered the proven acceptable ranges (PARs). The criticality of each process parameter and selection of IPCs to assure process control were determined using a risk-based approach based on process characterization data and platform knowledge.

Process parameter set points, normal operating ranges (NORs) and IPC ranges for each unit operation are established and identified in the batch records. Excursions outside the normal operating ranges are captured as deviations to the batch record. All deviations are assessed by Quality Assurance prior to batch disposition.

An overview of CPPs, IPCs and their corresponding acceptable ranges for the cell culture, harvest steps and purification steps of the lanadelumab process has been provided.

Changes in NORs within PARs are documented by the change control procedure and are not considered reportable. Changes outside PARs are handled via applications for variations, regardless of parameter criticality. Excursions outside NORs are captured as deviations for both critical and non-critical process parameters, and evaluated regarding impact to quality, safety and efficacy (the criticality is factored into the evaluation). For process parameters, the term ‘acceptable range’ is the same as the ICH ‘proven acceptable range’. IPC limits are either ‘acceptance criteria’ (rejection limits) or ‘acceptable ranges’ (action limits).

Control of materials

The raw materials have been sufficiently described.

The source, history and generation of the production cell line are well described.

The current cell banking system utilizes a two tier system consisting of a master cell bank (MCB) derived from the research cell bank (RCB) and a working cell bank (WCB) derived from a single vial of the MCB. Both the MCB and WCB were produced and tested according to cGMP regulations and ICH Q5A, Q5B and Q5D guidelines.

A post-production cell bank (PPCB) was prepared from one of the process performance qualification batches (PPQ2) and tested to ensure species identity, the absence of adventitious agent contaminants and genetic stability.

The overall approach and result of the cell bank testing is approvable.

Process validation

The process performance qualification (PPQ) studies were executed using the commercial process. The life-cycle of the lanadelumab process will be controlled through the process control strategy, release testing, stability monitoring and the continued process verification (CPV) program.

The process performance qualification of the manufacturing steps for active substance has been adequately described and reported. Attribute results were generally within PPQ acceptance criteria. The manufacturing process for active substance can be considered validated. Attributes identified for process monitoring, CQAs at a minimum, are trended periodically to support the continued process verification activities.

The information provided regarding characterisation and validation of resin reuse is sufficient and the resin reuse at-scale validation approach is acceptable.

The proposal for concurrent process validation of refiltration is acceptable.

In-process pool hold times are adequately validated.

The information provided regarding shipping validation is sufficient.

Manufacturing process development

The lanadelumab manufacturing process was developed in several steps. An overview of the different process versions has been provided.

During the upstream scale-up, the major change to the downstream process was increased number of cycles for the chromatography steps.

A major objection was raised regarding comparability between the clinical material and the commercial material. Additional data from extended characterisation, in-process controls, and short-term stressed stability studies (batch release data was submitted with the original application) was provided in response to the major objection and deemed satisfactory.

The comparability studies were performed according to ICH Q5E, and batches were compared based on routine in-process data, release testing, characterization testing, and short term stressed stability data with prospectively defined acceptance criteria.

In conclusion, based on the submitted data, comparability has been considered demonstrated for the process changes.

Control of critical steps and intermediates

The information provided regarding assigned CQAs and the control strategy is adequate. The quality attributes evaluated and the criticality summary have been provided.

Quality by Design (QbD) elements such as risk assessment and multivariate experimental design were used during process characterisation. Results from multivariate (and univariate) experiments were used to evaluate process parameter criticality, but parameter ranges were mainly established based on historical development and manufacturing and no design space is claimed. The terminology and definitions used for the control strategy elements is mainly in line with ICH Q8(R2)/Q9/Q10/Q11 as regards CQAs, CPPs and non-CPPs. The applicant considers CPP acceptable ranges to be proven acceptable ranges (PARs). This is acceptable.

Characterisation

Biochemical, biophysical, and biological characterisation of lanadelumab was conducted to provide a comprehensive understanding of the structural and functional properties and to enable an assessment of the criticality of product quality attributes.

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a monoclonal IgG1κ antibody.

An overview of process- and product-related impurities and contaminants and the tests used to detect them has been provided.

The approach to control residual DNA and protein A by in-process analyses and residual host cell protein (HCP) with the release specification is endorsed.

The purification process demonstrated sufficient and robust clearance of several bioreactor process-derived impurities.

Specification

The release and shelf life specification for the active substance has been established to ensure the identity, strength, purity, quality and safety of lanadelumab through its shelf life. The proposed specifications are consistent with ICH Q6B.

The analytical methods and the specifications were derived through the evaluation of (1) development experience, (2) characterization of the active substance and process validation data, (3) manufacturing history, release and ongoing stability data for active substance batches, and (4) toxicological and clinical evaluation of finished product manufactured with the active substance. In addition, compendia requirements for protein-based products were considered.

The commercial specification strategy focused on analytical data generated for active substance batches representing the validated commercial process.

HCP is below LOQ in all commercial scale batches, as analysed by a commercial kit. Given the batch data and the capability of the purification process to remove HCP from the active substance, the proposed limit seems reasonable.

The justifications for omitting residual DNA and protein A analyses from release testing are acceptable.

High mannose is classified as a critical quality attribute due to its possible impact to pharmacokinetics. It has been demonstrated that the level of high mannose is constant during long term storage of the active substance, manufacture of finished product and long term storage of finished product, thus a control for high mannose (man5 + man8) is included in the active substance specification. The proposed limit is acceptable considering that the levels of high mannose are in the low range when compared to other monoclonal antibodies, that the possibility of measurable differences in pharmacokinetics seems very low within the proposed range and that any potential negative effect on quality by high mannose levels in future batches is expected to be captured by other methods in the specification.

Even though the statistical approach chosen to set the specification limits (tolerance interval) is not fully supported, the levels of impurities are low and based on the presented data the specifications are found acceptable.

Analytical methods

All analytical procedures used for testing of the active substance are described in sufficient detail.

The potency is determined by measuring the equilibrium inhibition constant, Ki, for inhibition of human plasma kallikrein (pKal) activity. The result is reported in percent potency relative to a reference standard. The potency assay is also used as an identity test.

The use of a commercially available, generic HCP ELISA assay is considered acceptable in view of the low levels of residual HCP in the active substance. Additional data on the specificity of the generic HCP assay has been provided. It is noted that the applicant intends to replace the generic HCP ELISA by a process-specific assay.

Batch analyses

Batch data for all batches produced have been presented. Each batch was tested to the specification in place at the time of manufacture. Although some limits differ, the release data is reasonably consistent for all attributes.

Batch data from preclinical and clinical development batches is also presented. Overall, the batch release results seem consistent.

Reference materials

To date, three lanadelumab reference standards, one historical, one primary and one working standard, have been produced. Data from release testing and characterisation of the current primary and working reference standards have been presented and considered acceptable. Reference standards are re-evaluated annually.

Release testing, characterisation and annual retesting of future reference standards are described in the dossier. The approach is acceptable.

Information provided regarding the historical reference standard is sufficient.

Container closure

The active substance container closure system is a sterile USP Class VI polyethylene terephthalate glycol copolyester (PETG) square bottle (2000 mL) fitted with a high density polyethylene screw cap. The bottles and caps are received with a Certificate of Analysis issued from the vendor, pre-sterilized by gamma radiation, ready-for-use and require no further processing or cleaning. The container closure is composed of materials that are considered safe for use, and is compatible with the active substance.

Stability

The container closure systems for all batches in the stability studies are of the same material of construction as that used for the commercial active substance container closure system.

The stability studies are generally in compliance with ICH Q5C and the chosen analytical methods appear adequately stability indicating.

The proposed end-of-shelf life specification acceptance limits are the same as the release limits as no significant trends were found during stability testing.

Stability data generated at the long-term storage condition for the primary batches and for the supportive batches has been presented, as well as stability data at the accelerated temperature. The data supports the proposed commercial shelf life for the active substance.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is a solution for injection containing 300 mg of lanadelumab as active substance, at a concentration of 150 mg/ml. Each 300 mg vial is filled with a nominal volume of 2.0 ml of finished product. The vials are intended for total use.

Besides the active ingredient, lanadelumab, the composition comprises only compendial components (disodium phosphate dihydrate, citric acid monohydrate, histidine, sodium chloride, polysorbate 80, water for injections), typically used for formulating monoclonal antibodies, and is acceptable.

The primary packaging components consist of a Type I glass vial, a rubber stopper, and a crimp seal with cap. The materials in contact with the product comply with Ph. Eur. Two needles and one syringe are provided together in an administration kit that will be co-packaged with the finished product vial. The medical devices (needles and syringe) are CE marked.

An acceptable overview of the formulation development has been provided, including satisfactory data supporting the proposed composition.

The same finished product buffer formulation, although with different protein concentrations (100 mg/ml or 150 mg/ml), has been used throughout clinical studies and is proposed for commercial production.

The only difference in the finished product formulation from Phase 1 clinical supply to Phase 3 and commercial product is an increase in protein concentration from 100 mg/ml to 150 mg/ml. There was no change to the excipients in the formulation matrix from the Phase 1 clinical drug product to the Phase 3 and commercial product. The formulation of the finished product is identical to that of the active substance.

The Phase 1 studies were performed with a 100 mg/ml solution. The manufacturing process was transferred, including scale-up and change of concentration. This process, referred to as Version 1, was used for the Phase 3 studies. It was then further optimized to the commercial process, referred to as Version 2. PPQ was executed with the Version 2 process.

As a whole, the manufacturing process development has been described in sufficient detail. The results of process characterization studies were used to set the PARs. The development of the control strategy is generally well explained. The control strategy was based on CQAs, process characterisation, parameter impact assessment/parameter classification and process capability assessment.

Comparability studies were performed to assess the changes implemented during development.

The development of the primary container closure system has been sufficiently described in the dossier. Extractables/leachables studies were performed on the rubber stopper. Safety evaluation of the results confirm that all identified and quantified organic extractables have Human Daily Exposure values that are below the respective Tolerable Daily Intake when calculated for the maximum dose of 300 mg lanadelumab every 2 weeks.

Compatibility with the syringe and in-use stability for the finished product in the administration syringe has been demonstrated and is considered appropriate.

Manufacture of the product and process controls

The finished product is released by Shire Pharmaceuticals Ireland Ltd., Dublin, Ireland.

The manufacturing process and process controls have been presented. The manufacturing steps comprise receipt of frozen formulated active substance, storage, thawing, pooling and mixing, bioburden reduction filtration, redundant sterile filtration, filling, stoppering, capping, lot printing, visual inspection, bulk packaging, shipping, labelling, and packaging.

The batch numbering system has been described. The applicant proposes that the acceptable ranges for process parameters and IPCs are considered the PARs. This is acceptable. There is no reprocessing.

Only one process parameter, fill weight, has been identified as critical.

One in-process hold time has been defined and is related to hold of post-bioburden reduction filtered product. The proposed hold time is supported by PPQ results and is acceptable.

For the PPQ, consecutive full-scale batches of finished product were manufactured, including at least one minimum and one maximum batch size.

All results met the protocol acceptance criteria as well as the finished product release specification.

The presented validation of the aseptic processing is acceptable.

The proposed total time out of refrigeration (TOR) from the start of thawed active substance pooling to the end of finished product bulk packaging is supported by hold time challenges during PPQ and is acceptable.

Filter validation studies have been performed and included testing for microbial retention, product-specific bubble point, filter compatibility, lanadelumab antibody and polysorbate 80 binding, and extractables and leachables testing. A total product/filter contact time has been defined.

Results from shipping qualification studies and a simulated shipping study have been provided and are acceptable.

In conclusion, the process validation data are acceptable.

Product specification

Specification testing proposed for finished product batch release includes assays regarding the parameters identity, content, potency, purity and impurities and microbiological quantity tests as well as general properties tests.

The release specification for the finished product is the same as that of the active substance except for the finished product-specific compendial tests (extractable volume and attributes related to the container closure system).

Sterility is tested at release, while container closure integrity by dye ingress is performed on stability in lieu of sterility testing. This is acceptable. A test for polysorbate 80 was included upon request.

Analytical procedures

Several of the analytical procedures used for release and stability testing of finished product are also used for release and stability testing of the active substance. The non-compendial method specific to the control of finished product, i.e. the container closure integrity test, has been appropriately validated. Compendial methods have been appropriately verified for their intended use. A summary of analytical procedures modifications during development has been provided.

Batch analysis

Batch analyses data has been presented for batches of the 300 mg strength, manufactured at the commercial site from active substance manufactured at the commercial scale. All data presented complies with the proposed finished product specifications.

Batch analyses data is also provided for development batches.

In conclusion, the batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process.

Reference materials

The reference standard for testing of finished product is the same as described for active substance.

Stability of the product

The stability studies have been conducted in accordance with ICH at the recommended long-term storage condition of 5°C±3°C and accelerated condition. The primary stability batches include three PPQ lots and three development batches. These six batches are manufactured at the commercial site using processes representative of the full-scale commercial process and were stored in the container closure system proposed for marketing. The development batches are manufactured with the Version 1 manufacturing process; the PPQ batches are manufactured with the Version 2 process (i.e. commercial process).

After storage at the long-term storage condition of 5°C±3°C, test results for all product quality attributes are within the commercial specification.

Vials may be stored below 25°C for a single period of 14 days, but not beyond the expiry date.

The results of photostability studies demonstrate that lanadelumab is photosensitive at the ICH Q1B conditions. Therefore, the vials should be stored protected from light (i.e. in the outer carton).

In conclusion, a finished product shelf life of 24 months stored at 5°C±3°C is supported by the data provided.

Adventitious agents

No animal derived raw material is used in the manufacturing process other than the CHO-derived production cell line. Foetal bovine serum was used during development of the production cell line and the applicant has provided a TSE certificate of suitability issued by the EDQM.

The MCB, WCB and cells at the limit of in vitro cell age have been tested in accordance with ICH Q5A. Summary descriptions of the test methods used have been provided demonstrating the suitability of the respective methods.

The manufacturing process includes virus removal and inactivation steps. The ability of the purification process to remove virus was evaluated using model viruses. The reports from the virus clearance studies contain sufficiently detailed information to demonstrate compliance with ICH Q5A and CPMP/BWP/268/65. Data supporting the relevance of the down-scaled process steps as models for the commercial process has been presented in sufficient detail. The results provided also support the claimed viral clearance throughout the resin lifetime for the chromatography steps.

The data presented demonstrates effective reduction of a broad range of viruses. In addition, an acceptable safety margin has been demonstrated for retroviruses as requested by the guidelines.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

A major objection regarding comparability between the clinical and the commercial process versions was raised in during the procedure. Based on the additional data provided in response, it could be concluded that material from the different process versions can be considered comparable and consequently the major objection was considered resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant submitted a complete non clinical package to support the indication. The description of the non-clinical data assessed by the CHMP is mentioned below.

2.3.2. Pharmacology

In vitro

In vitro studies were conducted to characterize the nonclinical pharmacology of lanadelumab, including its binding to pKal, and its functional inhibition on pKal-induced generation of cHMWK and bradykinin. ELISA and fluorescence based assays demonstrated that lanadelumab-induced inhibition of pKal reduces both generation of bradykinin and hydrolysis of a synthetic Pro-Phe-Arg-AMC peptide reference substrate. The inhibition constant (K_i)-value for inhibition of human pKal-mediated hydrolysis of the reference substrate was about 0.125 nM. Lanadelumab was also a potent inhibitor of mouse, rat and cynomolgus monkey pKal with K_i-values of 0.300, 0.170 and 0.069 nM, respectively. In contrast, lanadelumab was about 100-fold less potent inhibitor for rabbit pKal (K_i=14.1 nM) compared to the other enzyme orthologues. A surface plasmon resonance based assay with various pKal active site-directed inhibitors and prekallikrein indicated that binding of lanadelumab to pKal include the active site of the enzyme with no affinity to prekallikrein. X-ray crystal structure analysis of the lanadelumab Fab-pKal complex revealed interactions between HCs CDR1, CDR3 and LC CDR2 and that the lanadelumab epitope includes both amino acids in the active site as well as residues in the vicinity of the active site. The specificity of lanadelumab for active pKal without lanadelumab proteolysis is mediated by the orientation of Hv CDR3 binding to the S1-3 substrate sites of pKal. Bioactivity of lanadelumab in human plasma pretreated with lanadelumab *in vitro* and in plasma of rats and cynomolgus monkeys treated with lanadelumab was monitored by a Western blot assay via inhibition pKal-mediated cleavage of HMWK to cHMWK following contact system activation. In both the human *in vitro* and rat and cynomolgus monkey *ex vivo* pharmacodynamic bioactivity assays lanadelumab protected complete cleavage of HMWK in a dose dependent manner.

In vivo

Due to the lack of established non-clinical animal models of HAE, the in vivo pharmacodynamics of lanadelumab was evaluated in the carrageenan-induced rat paw oedema model, in which bradykinin is a known proinflammatory mediator, and that can be used to access mechanistic aspects of pKal inhibition. In addition, of carrageenan to rat plasma in vitro has been shown to generate active pKal. Injection of carrageenan resulted in a maximum 2-fold increase in paw-volume 4 h after challenge. Lanadelumab pretreatment was found to inhibit carrageenan induced rat oedema in a dose-dependent manner with a maximum inhibition at 30 mg lanadelumab/kg by 73% following SC and 62% following IV infusion, respectively, suggesting an inhibition of pKal functional effects in vivo. Prophylactic inhibition of pKal appeared more effective than acute administration as the pharmacodynamic effect was more pronounced after SC dosing (24 h prior to carrageenan) as compared to IP administration (30 min prior to carrageenan) despite similar serum concentrations of lanadelumab (8 h post carrageenan).

This demonstrated the activity of lanadelumab, however, as the rat carrageenan paw oedema model is not a non-clinical model of HAE, efficacious doses in this model were not used to predict clinical efficacious doses, which is considered appropriate.

Secondary pharmacodynamics

The potential for lanadelumab to inhibit the non-target serine proteases (activated protein C, C1s, cathepsin G, Factor VIIa, Factor Xa, Factor XIa, Factor XIIa, granzyme B, hepsin, matriptase, neutrophil elastase, plasmin, thrombin alpha, tissue plasminogen activator, tissue kallikrein 1, tissue kallikrein 2, tissue kallikrein 5, tissue kallikrein 12, trypsin, urokinase) were evaluated *in vitro*. All these serine proteases sharing key active amino acids and catalytic mechanism with pKal were evaluated at lanadelumab concentrations ≥ 1µM. Lanadelumab did not inhibit any of the 20 evaluated serine proteases including FXIa, which is most similar to pKal (74% similar amino acid sequences between the full length proteins and 82% similarity between the catalytic domains). The expected C_{max} for lanadelumab in the highest and most frequent dose (300 mg 2qw patients in DX-2930-03) is 35 µg/mL (240 nM).

The potential of lanadelumab to induce antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) was evaluated using cultured human umbilical vein endothelial cells (HUVEC). Antibody-dependent cell-mediated cytotoxicity was measured using natural killer cells isolated from 3 different donors at effector-to-target cell ratios of 10:1. Complement-dependent cytotoxicity was performed using rabbit complement. Cell lysis was measured according to the release of the intracellular enzyme glyceraldehyde-3-phosphate dehydrogenase using a bioluminescent substrate. The primary positive controls for these experiments were 2 rabbit monoclonal antibodies against CD31, which induced ADCC and CDC in HUVEC. Rituximab was included as an additional positive control, which induced ADCC and CDC on target cells (Daudi B cells). Under these assay conditions, lanadelumab-mediated ADCC and CDC were not observed, which is considered appropriate. Dissociation constant (K_d) values for purified effector function receptors (Fcγ RI [CD64], Fcγ RIIA [CD32a], Fcγ RIIB/C [CD32b/c], Fcγ RIIIA [CD16a], Fcγ RIIIB [CD16b] and C1q determined by surface plasma resonance were equal to or lower than reported for other tested IgG antibodies. Based on the

combined *in vitro* characterization experiments conducted lanadelumab is not considered to be a high risk molecule for eliciting ADCC or CDC. A general secondary pharmacology profiling panel for off-target activity was not provided, which is acceptable for biologics. An in depth discussion on potential risks related to inhibition of pKal, particularly during long-term treatment with lanadelumab, based on experimental data and supporting references with focus on clot formation/ dissolution and potential consequences in humans was provided by the Applicant. Based on its indication (HAE) and mechanism of action (specific and incomplete pKal inhibition supporting a basal bradykinin generation) it is agreed that this discussion presented by the Applicant does not present any safety concerns in HAE patients. Long-term safety has been included as missing information in the RMP.

Safety pharmacology programme

Safety pharmacology studies with lanadelumab were integrated in the 4 week and 6 month repeat-dose toxicity studies performed in rat (function observational battery) and cynomolgus monkey (cardiovascular and respiratory). This approach follows the ICH Guidance S6 (R1) and is considered appropriate.

No effects on the functional and behavioural or respiratory parameters evaluated were observed.

In the 4 week SC toxicity study in cynomolgus monkey a mild reduction of heart rate detected by longer RR interval was observed in males dosed with 50 mg/kg/week at 19 to 22 hours following the day 28 dose. No concomitant changes in ECG parameters were detected in males (5 and 25 mg/kg) or females (5, 25 and 50 mg/kg). No effects on monitored blood pressure were noted.

Deficiencies in the timing of the recordings of the ECG parameters in relation to blood sampling for toxicokinetics as well as monitoring of blood pressure in restrained animals were detected. However, as the pharmacokinetic profile of lanadelumab is extended and the reduced heart rate observed in males of the 50 mg/kg group was transient and within the range of historical control data and no concomitant changes in the other ECG waveform or conduction parameters or blood pressure were observed in combination with absence of clinical signs or changes in behaviour patterns or body temperatures, this is not considered to be of toxicological significance. The applicant did not submit any *in vitro* safety studies such as hERG-channel testing. This is acceptable considering the nature of the drug product being a monoclonal antibody.

No lanadelumab related cardiovascular findings were observed in the 6-months study in cynomolgus monkey with an average C_{max} value of 744 µg/mL at study week 28 at the NOAEL of 50 mg/kg, providing a 21-fold exposure margin to expected maximum clinical exposure in HAE-patients treated with 300 mg lanadelumab by SC administration every 2 weeks. No cardiovascular effects were observed in the clinical trials conducted with lanadelumab.

Pharmacodynamic drug interactions

No dedicated pharmacodynamic drug interaction studies were conducted with lanadelumab. This is acceptable for an antibody that specifically targets pKal.

2.3.3. Pharmacokinetics

Pharmacokinetic/TK profiles of lanadelumab were evaluated following single- and repeat-dose SC administration in rats (4 weeks) and cynomolgus monkeys (4 weeks and 6 months). The PK/TK profile of lanadelumab was also evaluated in a 4-week IV infusion study in cynomolgus monkeys. Anti-drug antibody (ADA) response was measured in rats and cynomolgus monkeys and milk transfer was measured in the enhanced pre- and postnatal development (ePPND) study conducted in cynomolgus monkeys. Lanadelumab exposure was measured using enzyme-linked immunosorbent assays, solid phase extraction with acid dissociate and direct electro-chemiluminescent assays. These assays were designed to measure lanadelumab in rat and cynomolgus monkey plasma, and to measure antibodies to lanadelumab in rat and cynomolgus monkey plasma.

Methods of analysis

The used analytical methods appear to have been adequately characterized or validated and are considered suitable for determination of lanadelumab PK parameters, and anti-drug antibody levels where applicable.

Absorption

Pharmacokinetics of lanadelumab was evaluated in the rat following SC administration and in cynomolgus monkey following IV and SC administration. Lanadelumab exhibited typical PK behavior as expected from an IgG1 molecule: low clearance, low volume of distribution, and long half-lives in rats and cynomolgus monkeys, with SC bioavailability at approximately 66% in cynomolgus monkeys. In rats, lanadelumab was highly immunogenic, which resulted in the loss of exposure following repeated administration, limiting the utility of using rats for further toxicology studies, while immunogenicity was generally low in cynomolgus monkeys with both SC and IV routes of administration. The selection of the cynomolgus monkey as a single species for the pivotal 6-month toxicity study is endorsed.

Distribution

The estimated volume of distribution of lanadelumab was low, similar to plasma volume, which is consistent with the limited tissue distribution expected for an IgG mAb. Lanadelumab exhibited low (0.20%) milk transfer in cynomolgus monkeys.

Metabolism

No dedicated metabolism studies were performed and this is considered acceptable and in agreement with ICH S6(R1). The metabolic pathways of biotechnology-derived pharmaceuticals are generally understood and include degradation to small peptides and individual amino acids.

Excretion

As a monoclonal antibody, no urinary excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion of lanadelumab were performed.

2.3.4. Toxicology

The toxicity profile of lanadelumab has been evaluated in a toxicology program consistent with ICH S6. The pivotal toxicology studies were conducted in compliance with GLP regulations and standards. Rat and cynomolgus monkey were used as toxicology species based on *in vitro* pharmacology potency studies which indicated that pKal inhibition in rat and monkey was similar to human pKal inhibition.

The toxicology studies were performed with SC injection. Studies up to 4 weeks duration (with 4-week recovery) and 6 months were performed in rats and monkey respectively. Due to high anti-drug antibody (ADA) response in rats that reduced drug exposure, and combined with the apparent similarity in toxicity profile in rats and cynomolgus monkey, the cynomolgus monkey was selected as the single species for the pivotal 6-month toxicity study. In addition, a 4-week IV infusion study with 4 weeks of recovery was conducted in cynomolgus monkeys. Standard safety pharmacology endpoints were incorporated into the repeat-dose toxicology studies in rats (CNS) and cynomolgus monkeys (CV and respiratory). No genotoxicity or carcinogenicity studies have been performed. The routine battery of genotoxicity studies is not generally applicable to biotechnology derived products and a weight of evidence approach indicated low carcinogenic potential of lanadelubmab. The reproductive and developmental toxicity of lanadelubmab was evaluated in a ePPND study in monkey.

The toxicokinetics of lanadelumab has been characterized across all of the preclinical safety studies including the reproductive and developmental toxicity studies. The toxicokinetic profile of lanadelumab display low clearance and a long half-life which is expected for a IgG1 molecules. Across all repeat-dose toxicology studies, lanadelumab exposure was similar in male and female animals with the exception of the 4-week study in rats where a majority of animals were confirmed positive for ADAs.

Single-dose toxicity

Lanadelumab was well tolerated in rats and monkeys in single doses up to 50mg/kg SC in both species and 50mg/kg IV in monkey. An increase in APTT (up to 25%) was noted in both species. This can be considered a pharmacological effect of lanadelumab, which inhibits kallikrein, and is not considered adverse in the context of the single dose toxicology studies.

Repeat-dose toxicity

3 repeat-dose toxicity studies in rat and monkey have been performed with lanadelumab. Based on significant ADA-formation in the 4-week toxicity study in rats, the species was not used in longer term studies. Thus, the 6-month study in Cynomolgus monkey is the only longer term repeated-dose study in the program.

Rat

Mortalities

In the 4-week repeat-dose study in rats with exposure groups receiving lanadelumab doses 5, 25 or 50 mg/kg/week, one control group male was found dead on study day 22. One control group female and 1 female from the 5 mg/kg group died on study days 22 and 29, respectively. These deaths are considered unrelated to treatment with lanadelumab.

Additional findings

In the 4-week repeat-dose toxicity study in rats, there were reductions in body weight (2-6% which persisted after recovery (5-10%). However, the small magnitude of change is not considered a relevant effect, and was in fermales correlated with reductions in food intake. The increase in liver weight (8-10%), increase in liver enzymes (ALP (50%), AST (10%) and ALT (40%)) and the Kupffer cell hypertrophy in the lanadelumab treated groups are correlated and suggest a liver effect related to lanadelumab. Kupffer cell hypertrophy is seldom a spontaneous finding. It is often associated with test articles (or their carriers) wherein their physicochemical characteristics result in clearance from circulation by the Kupffer cells. However, there is no microscopic evidence of hepatocyte involvement. Because of the lack of microscopic evidence of hepatocyte injury and the recovery of the finding the issue is not further pursued.

An increase in APTT was noted in all lanadelumab treated animals (6-15% in both sexes). However, this finding, which was noted also in the single–dose studies, was not correlated with abnormal bleeding patterns. It can be considered an indirect pharmacological effect of lanadelumab because reduced kallikrein activity limits intrinsic coagulation pathway. An effect of lanadelumab on APTT was not noted in the repeat-dose studies in monkey.

Repeated SC administration in the rat resulted in a substantial decrease in exposure to lanadelumab in most animals at 25 and 50 mg/kg and some of the animals at 5 mg/kg. Indeed, 17/18 toxicokinetic animals were confirmed positive for positive for ADAs. Interestingly, ADAs were also noted in the control group but according to the Applicant there was no misdosing or contamination during collection or sample processing. Nevertheless, it can be concluded that the ADA formation has hampered the interpretability of the study, and the NOAEL value is not considered reliable. Accordingly, there is no valid NOAEL value from the repeat-dose toxicity studies in the rat.

Cynomolgus monkey

Mortalities

There were no mortalities in the monkey studies.

Additional findings

In the 4-week repeat-dose study in Cynomolgus monkey with exposure groups receiving lanadelumab doses 5, 25 or 50 mg/kg/week, transient serum chemistry and hematology effects were noted across groups without apparent systematicity. Enlarged ovaries and nodules were noted in the ovaries of treated females but not in controls. In addition, two females in the 50mg/kg/week dose group (one SD29 and one recovery) had cysts in the ovaries that were microscopically confirmed. However, ovarian cysts are commonly reported lesions in the cynomolgus macaque why the finding is not considered treatment related.

Longer RR interval (~30%) was noted on day 28 for males which generally demonstrated an expected inverse relationship to the potentially test article-related reduction in heart rate (~20% 22 hours post-dose). Considering the lack of concomitant changes in other cardiovascular parameters and clinical observations the

changes are not consideredof relevance. In addition, no safety issues related to changes in heart rate and longer RR interval have been reported in the clinical studies.

The 27 lanadelumab doses administered in the 6-month study in juvenile to adolescent cynomolgus monkeys (2.7-3.3 years) receiving lanadelumab doses 5, 25 or 50 mg/kg/week were well-tolerated. The only noteworthy finding in the study was mononuclear cell infiltrates that were noted at the injection site but also across various organs. While the infiltration was associated with degeneration at the injection site, the similarity in response across dose groups (including controls) suggests that the finding is procedure related. In addition, mononuclear (inflammatory) cell infiltration in various organs, including liver, kidneys, heart and lungs is a common histopathology finding in Cynomolgus monkeys.

Genotoxicity and carcinogenicity

No genotoxicity studies have been performed for lanadelumab in accordance with ICHS6. This is considered acceptable. The Applicant provided information for carcinogenicity risk assessment that takes into consideration the pharmacology, mechanism of action, scientific literature, data from chronic toxicity studies, and clinical experiences with lanadelumab as well as Kalbitor® (ecallantide). Based on the pharmacology and mechanism of action of lanadelumab, there is no concern for a pharmacologic or pathway-associated carcinogenicity risk. In a 2-year rat carcinogenicity study conducted with Kalbitor (ecallantide), a recombinant 60-amino acid peptide inhibitor of pKal, there were no test article-related neoplastic findings. Furthermore, no neoplastic or pre-neoplastic lesions or signs of immune suppression were observed in cynomolgus monkeys following 6 months of weekly dosing of lanadelumab. Based on this, it is acceptable to assume that the carcinogenicity risk of lanadelumab would be low. Thus, no further studies are considered necessary.

Reproductive and developmental toxicity

13-week repeat-dose fertility study

13-weeks of lanadelumab treatment at 10 or 50 mg/kg/week in cynomolgus monkey did not show adverse effects on fertility parameters in doses up to 50mg/kg/week. 5/6 ADA-positive animals showed comparable TK profiles to their group means. ADA-positive monkey at 10 mg/kg showed significantly lower systemic exposure. However, effects on the menstrual cycle (prolongation or arrest) were observed in 2/5 high-dosed females. The applicant was therefore requested to discuss the clinical relevance of these findings taking into account a potential pharmacology-driven effect of lanadelumab on female reproductive physiology. In the response, the Applicant indicated that menstrual cycle disruptions or stopping of menstruation can occur in some laboratory female Cynomolgus monkeys at the start of dosing. Historical control data were also provided to further support this statement. It is also noted that there was no histopathological finding associated with lanadelumab administration in the ovaries or uterus at any dose level in the 13-week fertility study, and there have been no reports of irregular menstruation in the clinical studies with lanadelumab. Thus, the overall data suggest that the effects (prolongation or arrest) on the menstrual cycle noted in 2 high dose animals may well be due to normal menstrual cycle irregularity rather than driven by lanadelumab treatment.

Enhanced pre- and postnatal developmental toxicity study

In an enhanced pre- and postnatal developmental toxicity study with lanadelumab at 10 or 50 mg/kg/week in Cynomolgus Monkeys, two maternal control animals and one maternal animal administered 10 mg/kg/dose were sacrificed in a moribund condition due to birth difficulties on GD 139, 169, and 160, respectively. The infants were stillborn. In addition, a number of additional infants were stillborn or sacrificed due to trauma or failure to thrive. However, the mortalities are not considered attributed to administration of lanadelumab. Overall 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. Mean plasma to milk ratio indicates a 0.20% milk transfer of lanadelumab from plasma post-partum.

However, while there is a 0.2% milk transfer of lanadelumab from plasma post-partum, it is unknown whether 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 infant cannot be excluded during this short period. Afterwards, lanadelumab could be used during breast-feeding if clinically needed. This information has been included in section 4.6 of the SmPC.

Other studies

Tissue Cross-Reactivity of Lanadelumab with Human Tissues in Vitro

In a tissue cross-reactivity study with lanadelumab with human tissues in vitro, specific lanadelumab staining was observed in multiple human tissues and consisted primarily of minimal to mild intensity cytoplasmic staining in endothelial cells and select nervous tissues in a variety of organs. However, tissue binding per se does not

indicate biological activity in vivo. In addition, it is not likely that the cytoplasm is accessible to the antibody *in vivo* why the relevance of the endothelial cell binding is uncertain.

To conclude, the toxicity profile of lanadelumab has been characterised in rat and Cynomolgus monkey in studies up to 6 months duration. The doses chosen are considered appropriate to characterise the toxicity of lanadelumab. Non-adverse toxicity findings in the SC studies include a treatment related but transient effect of heart rate and RR in monkey. While not observed in the clinical studies performed within this application, these are effects that may need further consideration. Infusion related effects were significant in animals across all dose groups in both species. However, this procedure related effect can be managed in the clinical situation. ADA development was prominent in the rat study, but less so in the cynomolgus monkey studies. While ADAs have been identified also in the clinical program, the data on ADA in animals are not reflective of the clinical situation.

2.3.5. Ecotoxicity / environmental risk assessment

The drug product is composed of naturally occurring amino acids, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore lanadelumab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

In repeat-dose studies evaluating once weekly SC injection in both rats (up to 28 days) and cynomolgus monkeys (up to 6 months) lanadelumab was well-tolerated at doses of up to and including 50 mg/kg (highest dose tested) with no organs of toxicity identified. Exposures in cynomolgus monkeys following 6 months of administration were approximately 23 fold greater than that noted at 300 mg q2 wks based on AUC.

Lanadelumab is not expected to interact directly with DNA or other chromosomal material, as it is made up entirely of naturally occurring amino acids and contains no inorganic or synthetic linkers or other nonprotein portions; therefore no genotoxicity evaluation has been conducted.

Carcinogenicity has not been evaluated in animals as based on the weight of evidence approach, lanadelumab is considered to have a low risk for carcinogenicity.

The effects of lanadelumab on fertility were evaluated in sexually mature cynomolgus monkeys. In a 13 week study, once weekly SC administration of lanadelumab had no effects on male or female fertility at doses of 10 or 50 mg/kg (highest dose tested). Exposures in sexually mature cynomolgus monkeys in the fertility study were approximately 21 fold greater than that noted at 300 mg q2 wks based on Cmax and AUC, respectively.

In the ePPND study in pregnant cynomolgus monkeys administered once weekly doses of 10 or 50 mg/kg (highest dose tested), there were no lanadelumab-related effects on pregnancy and parturition, embryo foetal development, survival, growth, and/or postnatal development of offspring. Exposures in the ePPND study were approximately 32 fold greater than that noted at 300 mg q2 wks based on AUC.

2.3.7. Conclusion on non-clinical aspects

Non-clinical data reveal no special hazard for humans. There are no objections to approval of lanadelumab from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Clinical development program

Study	Randomized Population	N	Study Design	Treatment Groups and Number of Subjects Randomized	Treatment Duration
Key efficacy study					
DX-2930-03 (HELP) Phase 3	HAE subjects (Type I or II) Age:≥12	125	Multicentre, randomized, double-blind, placebo-controlled	Lanadelumab: 150 mg q4wks (n=28), 300 mg q4wks (n=29), 300 mg q2wks (n=27) or placebo q2wks (n=41)	6 months (13 doses over 26 weeks)
Supportive efficacy studies					
DX-2930-04 (HELP Study Extension) Phase 3	HAE subjects (Type I or II) Age: ≥12 Rollover from Study DX-2930-03 Non-rollover subjects	212 109 103	Multicentre, open-label extension	Lanadelumab 300 mg q2wks[a]	30 months (maximum of 66 doses over 132 weeks)
DX-2930-02 Phase 1b	HAE subjects (Type I or II) Age: ≥ 18	37	Randomized, double-blind, placebo-controlled, multiple ascending dose	Lanadelumab 30, 100, 300 or 400 mg or placebo	2 doses, 14 days apart

Abbreviations: HAE=hereditary angioedema; q2wks=every 2 weeks; q4wks=every 4 weeks; SC=subcutaneous; y=years

[a] Rollover subjects (participated in DX-2930-03) received their first open-label dose on Day 0 with Dose 2 being administered at the time of their first HAE attack. Subsequent doses for rollover subjects were administered every 2 weeks. Non-rollover subjects (did not participate in DX-2930-03) received lanadelumab every 2 weeks.

2.4.2. Pharmacokinetics

Pharmacokinetic data for lanadelumab are available from four clinical studies; a Phase 1a, single ascending dose study in healthy volunteers, a Phase 1b multiple ascending dose in HAE patients, the pivotal placebo-controlled Phase 3 study (6 months of treatment) and a supportive, open-label Phase 3 extension study.

Methods

Rich pharmacokinetic sampling for lanadelumab concentrations was performed in the Phase 1 study in healthy volunteers (DX-2930-01), and the data was analysed using non-compartmental methods. Sparse pharmacokinetic sampling was performed in the three studies in HAE patients (Phase 1b study DX-2930-02, and Phase 3 studies DX-2930-03 and DX-293004) and the data was primarily analysed by population PK modelling.

Two different ELISA assays for determining lanadelumab concentrations in plasma have been used during the clinical development of lanadelumab, one was used to analyse samples from the study in healthy volunteers and one for the samples from the studies in HAE patients. Both methods were adequately validated and showed acceptable performance during analysis of study samples.

The ADA analysis strategy included an initial screening step, followed by confirmation, titer determination, and evaluation of neutralizing activity for all positive samples. The screening, confirmatory, and titration methods employ an antibody-bridging design which is expected to detect all isotypes of anti-lanadelumab antibody.

Absorption

After subcutaneous (SC) administration, lanadelumab is slowly absorbed with a T_{max} of 6-7 days. Absolute bioavailability after SC administration has not been determined. Preferred injection site (arm, thigh or abdomen) or self-administration vs. administration by health care professionals had no relevant effect on bioavailability.

Between Phase 1 and Phase 3 in the clinical development, there was a change in the contract manufacturer responsible for supplying drug substance and drug product. The drug product used in Phase 3 was similar to the proposed commercial product. A comparability assessment made including Quality and Non-clinical data, and the products were considered comparable.

Distribution

Volume of distribution cannot be determined as F is not known. Lanadelumab is likely not largely distributed outside the vascular space. In the population PK model, the typical value for Vc/F was 12.8 L, and body weight was a significant covariate for Vc/F.

Elimination

No studies have been performed to characterise the elimination mechanisms of lanadelumab. Lanadelumab metabolism and elimination are expected to follow the normal immunoglobulin clearance pathways, resulting in degradation to small peptides and amino acids.

After administration of single-dose of 0.1 – 3.0 mg/kg to healthy volunteers, the mean elimination half-life of lanadelumab was 17 to 21 days with no apparent dose dependency. In the final population PK model, including data from all four clinical studies, the typical steady state elimination half-life of lanadelumab was 15 days and the population estimates of typical CL/F was 25 ml/h. The estimated half-life is consistent with that observed for other monoclonal antibodies.

Linearity

There was no obvious non-linearity in lanadelumab pharmacokinetics after single dose administration of doses of 0.1 – 3.0 mg/kg, or after two repeated, flat doses of 30 – 400 mg. There was no apparent change in pharmacokinetics over time at repeated administration of 150 mg q4wks, 300 mg q4wks or 300 mg q2wks.

Special populations

There are no specific studies in subjects with renal or hepatic impairment, which is acceptable for an antibody, as renal or hepatic impairment are not expected to relevantly alter antibody exposure.

In the population pharmacokinetic analysis, weight was shown to be a significant covariate for lanadelumab CL/F and Vc/F. Low-weight and high-weight patients are predicted to have a higher and lower exposure, respectively, than the average 70 kg patient.

Due to a generally lower body weight, adolescents are by population pharmacokinetic analysis predicted to have a somewhat higher (on average <40% higher) exposure than the average adult patient. The observed mean AUC tau,ss values for adults and adolescents (N=21) were 460 and 629 µg*h/ml, respectively, confirming an about 37% difference. The model-predicted AUC range in the study population, based on a weight range of 178 kg to 37 kg, is about 200-900 µg*d/ml. The observed AUC range was 121-832 ug*d/ml in adults and 321-1050 ug*d/ml in adolescents. The maximum individual AUC in adolescents was, thus, approx. 30% larger than the maximum individual AUC in adults

After correcting for body weight, age or gender had no apparent effect on lanadelumab exposure. Data are too limited to draw conclusions on the effect of race on lanadelumab pharmacokinetics.

Interactions

There is no specific pharmacokinetic *in vitro* or *in vivo* interaction data for lanadelumab. Pharmacokinetic interactions are not expected for an antibody without cytokine effects.

2.4.3. Pharmacodynamics

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent episodes of oedema predominately affecting the skin, digestive tract, and upper airway. The pathophysiological background to HAE is either a deficiency (HAE 1) or a dysfunction (HAE2) of C1-esterase inhibitor (C1-INH), leading to dysregulation of plasma kallikrein activity. A third entity, “HAE with normal C1-INH”, formerly called HAE 3, has been identified. This group is believed to be heterogeneous and at least three different gene mutations leading to HAE with normal C1-INH have been identified.
Lanadelumab is a monoclonal antibody designed to inhibit active plasma kallikrein proteolytic activity which in turn prevents the release of bradykinin from high molecular weight kininogen (HMWK), thereby preventing the vascular leak and swelling during an angioedema attack that is initiated when bradykinin binds to the B2 receptor.
Available and authorized drugs target the same pathway, including the same target for ecallantide, used in the acute treatment of HAE attacks in US. Of note, the overall B/R of ecallantide was considered negative by the CHMP in 2011.

Mechanism of action

Lanadelumab is a recombinant, fully human immunoglobulin G (IgG) 1 kappa light chain monoclonal antibody that inhibits plasma kallikrein (pKal) proteolytic activity without binding prekallikrein, the inactive precursor found in the circulation. Increased pKal activity leads to angioedema attacks in patients with hereditary angioedema (HAE) through the proteolysis of high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. It has been demonstrated that patients with HAE due to C1-inhibitor (C1-INH) deficiency or dysfunction have increased pKal activity, as indirectly measured by amount of cHMWK, both during and in between HAE attacks.

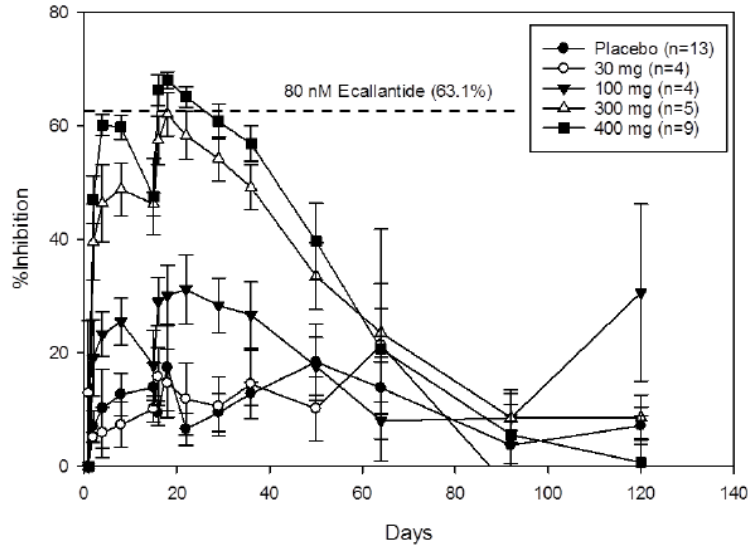
Primary pharmacodynamics

The pharmacodynamic effect was assessed by two assays; a plasma kallikrein activity assay and a Western blot assay measuring the cleavage of HMWK.

DX-2930-01 was a first-in-human, double-blind, placebo-controlled, Phase 1a, single-ascending dose study evaluating a single dose of lanadelumab (0.1, 0.3, 1.0, or 3.0 mg/kg) in 32 healthy adult subjects.
There was a dose-dependent inhibition of plasma kallikrein activity by lanadelumab 1 mg/kg (approx. 19% inhibition from baseline and 3 mg/kg (approx. 36%) but not by 0.1 or 0.3 mg/kg in healthy subjects. Furthermore, the highest dosing of lanadelumab, 3.0 mg/kg, reduced the levels of cleaved high molecular weight kininogen (cHMWK) from (mean [SD]) 53.9 [10.7] to 28.1 [7.4] at Day 5 (p=0.001).

DX-2930-02 was a double-blind, placebo-controlled Phase 1b multiple-ascending dose study evaluating 2 injections of lanadelumab (30, 100, 300 or 400 mg) separated by 2 weeks in 37 adult subjects with HAE. Lanadelumab 100, 300 and 400 mg induced a dose-dependent plasma kallikrein inhibition of approx. 30%, 60%, and 70%, respectively. No effect compared to placebo was seen with 30 mg lanadelumab. Following the second dose of lanadelumab, the 300 and 400 mg dose groups demonstrate levels of plasma kallikrein inhibition comparable to that observed following the ex vivo plasma addition of 80 nM ecallantide, a plasma kallikrein inhibitor approved in the US for treatment of acute angioedema attacks due to HAE.
Pre-dose plasma obtained from the HAE subjects contained approximately 52% cHMWK in contrast to approximately 8% in subjects without HAE in study DX-2930-01 contained cHMWK. Lanadelumab 300 and 400 mg reduced cHMWK levels on Day 8 and 22 with a maximum reduction at Day 22. In these dose groups, the level of cHMWK approached that observed in healthy subjects (8.3%). No significant effect of lanadelumab on cHMWK was seen later in this study; however, only two doses of lanadelumab, Day 0 and Day 14, were given.

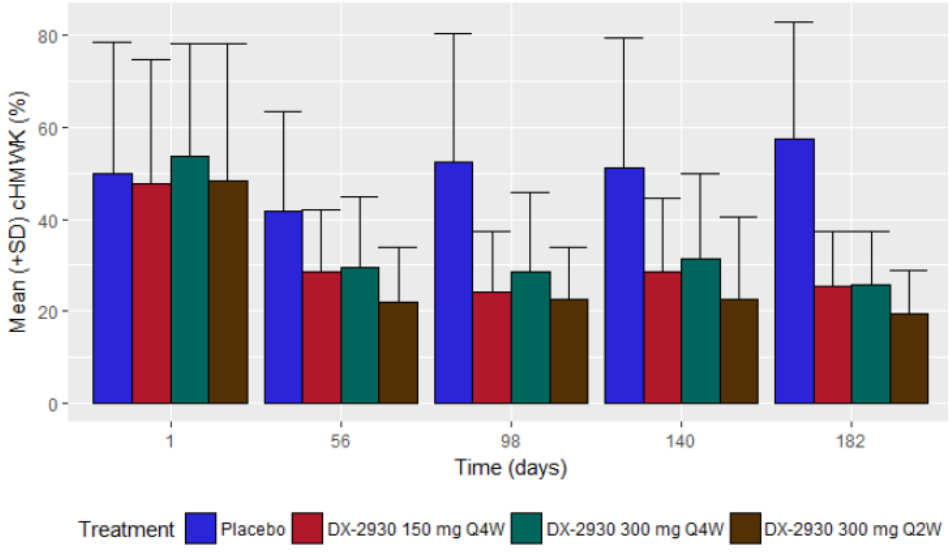
Figure 1 Pharmacodynamic Effect of DX-2930 (lanadelumab) in HAE Subjects Based on Fluorogenic Assay—PD Population, Study DX-2930-02



No dose between 100 and 300 mg has been studied whereas 3.0 mg/kg shows a significant response.

DX-2930-03 was a double-blind, placebo-controlled Phase 3 study evaluating 3 dose regimens (150 mg every 4 weeks [q4wks], 300 mg q4wks, 300 mg q2wks) in subjects aged 12 years and older with HAE. 125 subjects received at least 1 dose of study treatment.
Only descriptive data are provided (Figure 2). Numerically, levels of cHMWK are reduced in all lanadelumab treatment arms compared to placebo.

Figure 2 Mean (+SD) Levels of cHMWK versus Time by Treatment Over Treatment Period (Study DX-2930-03)



DX-2930-04 is an ongoing open-label extension study evaluating repeated 300 mg doses for up to 132 weeks in subjects aged 12 years and older with HAE who either previously received lanadelumab in Study DX-2930-03 (rollover subjects) or were previously untreated (non-rollover subjects).

The results in rollover subjects treated with placebo in study DX-2930-03 and non-rollover subjects were comparable to the results in DX-2930-03. In rollover subjects treated with lanadelumab in study DX-2930-03, the cHMWK reduction was similar day 0 and day 192.

Secondary pharmacodynamics

The potential of lanadelumab to inhibit other serine proteases were tested. No inhibition was detected in any of the 20 serine proteases tested, including Factor IXa which is the most similar to plasma kallikrein.

Effect of antidrug antibody or neutralizing antibody on pharmacodynamics

For the neutralizing anti-lanadelumab antibody (NAb) assay, the applicant computed a cut-point with only 0.1% false positive (Table 2) allowed instead of the usual 1% rejection threshold. The use of this tighter false-positive coefficient increases the rate of false-negative results and is not recommended. A report with data using a cut point of 1 % was provided on request. This resulted in 3 new subjects with the presence of neutralizing ADAs over the rejection threshold giving a total of 10 subjects (4,5%) over the two Phase III studies as compared with 7 subjects (3,2%) using the 0.1% cut-off (Table 3).

Table 2 Summary of Immunogenicity Response *Using 0.1% False-Positive Cut Point For Neutralizing ADA Antibody Assay* — Lanadelumab-treated Population

Time point Category of result	150 mg q4wks ↓ 300 mg q2wks N=28 n (%)	300 mg q4wks ↓ 300 mg q2wks N=29 n (%)	300 mg q2wks ↓ 300 mg q2wks N=27 n (%)	Placebo ROs and Nonrollovers N=136 n (%)	Lanadelumab-treated Population N=220 n (%)
ADA prevalence[a]	7 (25.0)	4 (13.8)	5 (18.5)	10 (7.4)[f]	26 (11.8)
ADA incidence[b]	7 (25.0)	4 (13.8)	4 (14.8)	10 (7.4)[f]	25 (11.4)
Pre-existing ADA	0	1 (3.4)	2 (7.4)	0	3 (1.4)
Treatment-induced[d]	7 (25.0)	3 (10.3)	3 (11.1)	10 (7.4)	23 (10.5)
Treatment-boosted[e]	0	1 (3.4)	1 (3.7)[g]	0	2 (0.9)
Non-neutralizing ADA	4 (14.3)	3 (10.3)	5 (18.5)	7 (5.1)	19 (8.6)
Neutralizing ADA	3 (10.7)	1 (3.4)	0	3 (2.2)	7 (3.2)

Table 3 Summary of Immunogenicity Response *Using 1% False-Positive Cut Point For Neutralizing ADA Antibody Assay* - Lanadelumab-treated Population

Time point Category of result	150 mg q4wks ↓ 300 mg q2wks N=28 n (%)	300 mg q4wks ↓ 300 mg q2wks N=29 n (%)	300 mg q2wks ↓ 300 mg q2wks N=27 n (%)	Placebo ROs and Nonrollovers N=136 n (%)	Lanadelumab-treated Population N=220 n (%)
ADA prevalence[a]	7 (25.0)	4 (13.8)	5 (18.5)	10 (7.4)[f]	26 (11.8)
ADA incidence[b]	7 (25.0)	4 (13.8)	4 (14.8)	10 (7.4)[f]	25 (11.4)
Pre-existing ADA	0	1 (3.4)	2 (7.4)[h]	0	3 (1.4)[h]
Treatment-induced[d]	7 (25.0)	3 (10.3)	3 (11.1)	10 (7.4)	23 (10.5)
Treatment-boosted[e]	0	1 (3.4)	1 (3.7)[g]	0	2 (0.9)
Non-neutralizing ADA	4 (14.3)	3 (10.3)	~~5~~ *4* (~~18.5~~ *14.8*)	~~7~~ *5* (~~5.1~~ *3.7*)	~~19~~ *16* (~~8.6~~ *7.2*)
Neutralizing ADA	3 (10.7)	1 (3.4)	~~0~~ *1 (3.7)*	~~3~~ *5* (~~2.2~~ *3.7*)	~~7~~ *10* (~~3.2~~ *4.5*)

ADA=antidrug antibody; n=number of subjects experiencing the event

[a] Prevalence is defined as the proportion of study population having drug-reactive antibodies (including pre-existing antibodies) at any time point.

[b] Incidence is defined as the proportion of study population found to have seroconverted or boosted their pre-existing ADA during the study period.

[c] Pre-existing ADA refers to a signal detected prior to treatment.

[d] Treatment-induced responses are characterized by a negative pretreatment sample with at least one positive sample at a subsequent time point.

[e] Treatment-boosted responses are characterized by a positive pretreatment sample that are boosted to a higher level following drug administration.

[f] Includes 2 placebo-treated subjects who had ADA-positive samples in Study DX-2930-03. The 2 subjects rolled over in Study DX-2930-04 and all blood samples were negative for ADA in Study DX-2930-04.

[g] One additional subject with pre-existing ADA had a positive sample post-dose, however since the titer was the same as the pretreatment sample it was not considered to be "treatment-boosted".

[h] *One subject with pre-existing ADA had antibodies classified as neutralizing at baseline.*

Source: Module 5.3.5.1, DX-2930-03 CSR, Table 14.3.4.8.2; Module 5.3.5.2, DX-2930-04 Interim CSR, Table 14.3.4.8.2; *data on file*; Shankar et al., 2014.

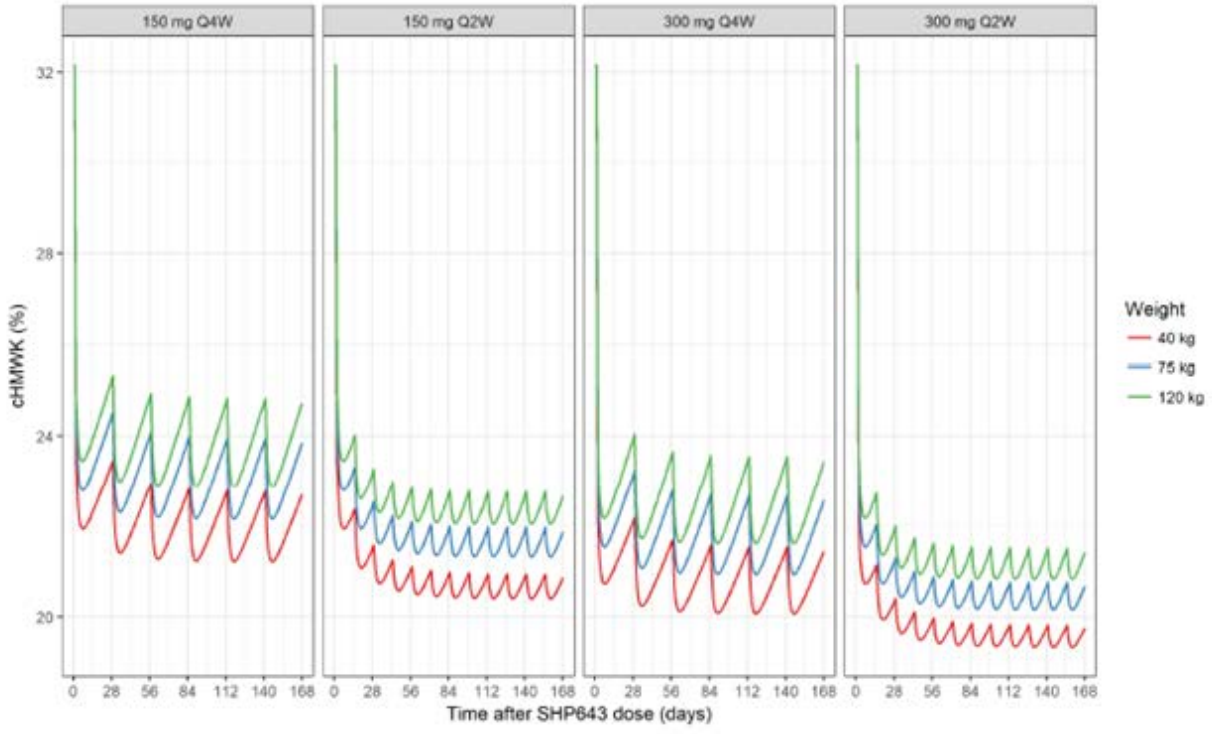
There was no apparent impact on the efficacy, pharmacokinetic, or pharmacodynamic profile of lanadelumab due to the presence of antibodies classified as neutralising with either cut-off. No subject discontinued treatment with lanadelumab or reported an AE indicative of a hypersensitivity reaction due to the presence of ADA classified as neutralising.

Relationship between plasma concentration and effect

Efficacy

Population PK/PD models were constructed to describe the relation between lanadelumab exposure and plasma kallikrein response (pKal) as well as high molecular weight kininogen (cHMWK). The latter model was used to predict the cHMWK time profiles at different dosing schedules and in patients of different weight (Figure 3).

Figure 3. Predicted cHMWK time profiles following repeated subcutaneous dosing of lanadelumab in different dosing schedules in typical patients of 40, 75 and 120 kg.



Safety

The relationship between lanadelumab exposure parameters and different safety parameters was also evaluated. No strong or significant correlations were observed between lanadelumab exposure and liver function tests, haematological parameters including aPTT, or cardiovascular parameters, respectively. There is therefore not apparent indication of a higher risk of systemic adverse events at a higher exposure.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetic evaluation of a new active substance should aim at characterising the pharmacokinetic properties of the substance, in order to possibly support the proposed dose regimen and to predict situations and patient groups where exposure may be clinically significantly different from that in the pivotal efficacy/safety study population. Evaluation of exposure-response and/or exposure-toxicity relationships may aid estimation of what is a clinically relevant difference in exposure. Lanadelumab is an antibody, and some aspects of the pharmacokinetic behaviour can therefore be predicted without specific studies, such as elimination mechanisms and the potential for pharmacokinetic drug-drug interactions.

Overall, the clinical pharmacology data package for lanadelumab, with plasma concentration data from one ascending single-dose study in healthy volunteers and three repeated-dose studies in HAE patients, and analysis primarily by population PK modelling, is considered relevant for an antibody.

Plasma concentration data from study DX-2930-03 indicate that one patient in the placebo group was administered one dose of lanadelumab, with lanadelumab concentrations on day 56 in the same range as

patients receiving a 300 mg dose. According to the applicant this was due to an unintentional mix-up of study product and the patient was not included in the efficacy analysis. As there are no signs of systematic mis-dosing or mix-up, this single case is of no concern for the overall interpretation of the pharmacokinetic data.

The ADA and Nab assays were clearly described and adequately validated. Long term stability testing is ongoing and will be reported post approval which was considered acceptable. The neutralizing antibody (Nab) assay is considered adequately validated. The Applicant originally computed a cut-point with only 0.1% false positive allowed instead of the usual 1% rejection threshold. In response to questions, the presence of neutralising anti-lanadelumab antibodies was re-calculated using a 1% false positive rate. This resulted in three additional subjects with the presence of neutralising ADAs over the rejection threshold giving a total of 10 subjects (4,5%) in the two Phase III studies as compared with 7 subjects (3,2%) using the 0.1% cut-off.

The comparability between the Phase 1 and Phase 3 products and the Phase 3 and commercial products has been clarified and it is agreed by CHMP that the products can be considered comparable. Thus, no clinical comparability data is necessary.

The estimated steady state half-life of 15 days supports the proposed q4w or q2w dosing. In line with linear pharmacokinetics, the $AUC_{0\text{-}2weeks}$ at dosing with 300 mg q2w was similar to the $AUC_{0\text{-}4weeks}$ at dosing 300 mg q4w.

No studies have been performed to characterise the elimination mechanisms of lanadelumab, which is acceptable. Also lack of dedicated pharmacokinetic studies in patients with renal or impairment and lack of *in vitro* data on protein binding and active transport is acceptable for an antibody. There is no *pharmacokinetic* concern for patients with renal or hepatic impairment, i.e. a concern for increased exposure. Whether patients with renal or hepatic impairment might be more susceptible to adverse events at normal exposure is discussed later in the report.

Weight was a significant covariate for lanadelumab CL/F and Vc/F. The heaviest patient included in clinical studies weighed 178 kg and was predicted to have a lanadelumab AUC less than half of the AUC in a 70 kg patient, while the lightest patient, a 37 kg adult, was predicted to have a < 50% increase in AUC. Adolescents are predicted to have an on average < 40% higher exposure than the average adult patient. The chosen flat dose regimen may, thus, lead to a relatively high variability in exposure. Indeed, the individual observed AUC values in the study populations varied by almost 7-fold in adults and by more than 3-fold in adolescents. Variability in exposure of an active substance is not by itself a concern if the exposure range is within the therapeutic window from an efficacy safety as well as a safety point of view.

The applicant made a subgroup analysis demonstrating overall adequate efficacy in patients > 100 kg. However, there were relatively few patients in this group, it included a wide body weight range and at the lowest tested dose (150 mg q4w), there was a possible trend towards lower efficacy in the highest weight group. Thus the applicant did no longer pursued the 150 mg q4w dose as a dosing alternative in the SmPC.

The effect of weight appears not to be of concern for efficacy of the remaining alternatives, 300 mg q2w or 300 mg q4w. Considering the safety profile and the PKPD data indicating no clear correlation between exposure and systemic adverse events, the higher mean AUC in adolescents as compared with the adult population might not be a concern for safety. Discussion on the posology is provided later in the efficacy section.

The lack of evaluation of pharmacokinetic drug interaction potential is acceptable for an antibody. The disposition of lanadelumab is not expected to be dependent on metabolising enzymes or transport proteins. Direct effects of an antibody on metabolism or transport of other drugs are also not expected. Lanadelumab is

not reported to affect cytokine levels, and therefore secondary effects on cytokine inhibition of CYP activity are not anticipated.

Pharmacodynamics

In HAE type 1 and 2, plasma kallikrein activity is dysregulated due to the absence or dysfunction of C1-esterase inhibitor (C1-INH).
Lanadelumab is a monoclonal antibody designed to inhibit active plasma kallikrein proteolytic activity. The dose dependent inhibition of plasma kallikrein activity by lanadelumab correlating with lanadelumab plasma concentrations seen in the two phase 1 studies DX-2930-01 (healthy subjects) and DX-2930-02 (HAE subjects) is therefore considered to indicate a drug effect on the intended target molecule.

Loss of inhibition of plasma kallikrein activity leads to increased bradykinin release from high-molecular weight kininogen (HMWK) and thereby vascular leak mediated by bradykinin binding to the B2 receptor (B2-R) on the surface of endothelial cells. In both studies, there was a dose-dependent reduction of the cHMWK levels. The use of cHMWK as a marker for bradykinin levels is accepted and a putative role for lanadelumab in reducing HAE attacks is therefore considered supported.
A clinical relevance of these results was supported by an ad hoc analysis in study DX-2930-02, which demonstrated an association between lanadelumab drug exposure and prevention of angioedema attacks as discussed in later in this report.

In the proof of concept study DX-2930-02, no dose between 100 and 300 mg has been studied whereas 3.0 mg/kg (the highest dose evaluated in study DX-2930-01) shows a significant response.
3.0 mg /kg corresponds to 120 mg for an adolescent weighing about 40 kg and to 150 to 240 mg for an adult weighing 50 to 80 kg. The dosage of 150 mg should have been evaluated in the phase 2 study and, if relevant, as 150mg q2w in the phase 3 study; only 3 patients were < 50kg in the phase 3 study.

The pharmacodynamic results from the two phase 3 studies are largely consistent with the results of the phase 1 studies. In pivotal study DX-2930-03, only descriptive data are provided. Numerically, levels of cHMWK are reduced in all lanadelumab treatment arms compared to placebo.

The overall incidence of ADA with lanadelumab treatment was 11.4% (25/220). A total of 7 (3.2%) subjects tested positive for low titre antibodies classified as neutralizing.
There was no impact on pharmacodynamic profile of lanadelumab in any of the phase 3 studies due to the presence of antibodies classified as neutralizing. However, the low number of subjects should be remembered. In this context, it is of interest that lanadelumab induced neutralising ADA in up to 79% of exposed rodents in preclinical studies. The effect was dose-dependent.

The PKPD model for cHMWK is considered acceptable for evaluation of the relationship between exposure and efficacy, while the other exposure-efficacy models have not been shown to perform adequately.

2.4.5. Conclusions on clinical pharmacology

The Clinical Pharmacology data for lanadelumab are overall considered sufficient and have been adequately demonstrated.

There was a clear effect of body weight on lanadelumab clearance. The proposed flat dosing regimen will lead to a relatively high variability in exposure, but the exposure range with the proposed dosing regimen, 300 mg q2w, might be expected to be within the therapeutic window for adolescents as well as for adults. The benefit of having a flat dosing regimen from a self-administration point of view is acknowledged.

However, in patients who are stably attack free, the possibility to reduce the dose regimen (e.g. 300mg Q4w) was considered beneficial by CHMP, especially for patients with low body weight (less than 50 kgs). This is based on the clinical efficacy data and is therefore introduced in the posology section of the SmPC.

Plasma kallikrein activity and cHMWK levels were reduced by lanadelumab in a dose-dependent way. So far, no impact on pharmacodynamic profile by neutralising antidrug antibodies was seen.

The SmPC adequately reflects the Clinical Pharmacology data.

2.5. Clinical efficacy

The proposed indication of routine prophylaxis to prevent attacks and control the symptoms of HAE in patients 12 years and older is based on the efficacy results from a single pivotal double-blind placebo controlled Phase 3 study (Study DX-2930-03), supportive efficacy data, including durability of response, from the on-going open-label Phase 3 study (Study DX-2930-04), and the proof of concept from the Phase 1b multiple ascending dose trial (Study DX-2930-02).

Table 4 Clinical development program

Study	Randomized Population	N	Study Design	Treatment Groups and Number of Subjects Randomized	Treatment Duration
Key efficacy study					
DX-2930-03 (HELP) Phase 3	HAE subjects (Type I or II) Age:≥12	125	Multicentre, randomized, double-blind, placebo-controlled	Lanadelumab: 150 mg q4wks (n=28), 300 mg q4wks (n=29), 300 mg q2wks (n=27) or placebo q2wks (n=41)	6 months (13 doses over 26 weeks)
Supportive efficacy studies					
DX-2930-04 (HELP Study Extension) Phase 3	HAE subjects (Type I or II) Age: ≥12 Rollover from Study DX-2930-03 Non-rollover subjects	212 109 103	Multicentre, open-label Extension	Lanadelumab 300 mg q2wks[a]	30 months (maximum of 66 doses over 132 weeks)
DX-2930-02 Phase 1b	HAE subjects (Type I or II) Age: ≥ 18	37	Randomized, double-blind, placebo-controlled, multiple ascending dose	Lanadelumab 30, 100, 300 or 400 mg or placebo	2 doses, 14 days apart

Abbreviations: HAE=hereditary angioedema; q2wks=every 2 weeks; q4wks=every 4 weeks; SC=subcutaneous; y=years

[a] Rollover subjects (participated in DX-2930-03) received their first open-label dose on Day 0 with Dose 2 being administered at the time of their first HAE attack. Subsequent doses for rollover subjects were administered every 2 weeks. Non-rollover subjects (did not participate in DX-2930-03) received lanadelumab every 2 weeks.

2.5.1. Dose response study (DX-2930-02)

Study title :

A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX-2930 in Hereditary Angioedema Subjects.

Methods

Study design

The study design of study DX-2930-02 is summarised in Table 4 above.

The range of lanadelumab dosing for the clinical development program was based upon estimation of the level of plasma kallikrein inhibition necessary to attain effective prophylaxis against HAE attacks.
Ecallantide is a biologic plasma kallikrein inhibitor approved in the US to treat acute HAE attacks. The maximum plasma concentration (Cmax) obtained following ecallantide administration is approx 586 ng/mL or 83 nM. Conservative estimates of the amount of plasma kallikrein required to prevent an attack may equal that needed to treat an acute attack. Based on this, doses 0.1-3.0 mg/kg were used in the phase 1 first-in-human study in healthy subjects DX-2930-01.

A conservative starting dose of 30 mg per dose was planned, with escalation to 100 and then 300 mg in a flexible dose-escalation scheme. Each cohort nominally consisting of 6 subjects randomised 2:1 to active drug and placebo.
The flexible dose-escalation scheme allowed escalation to dose higher than 300 mg (up to a maximum of 400 mg), if necessary, and if supported by the cumulative safety results. This resulted in the addition of 2 additional cohorts, in which subjects were randomized 2:1 to receive either placebo or 400 mg lanadelumab.

Main eligibility criteria

The main inclusion criteria were subjects ≥ 18 years of age with HAE type I or II. Subjects must also have been experiencing ≥ 2 HAE attacks per year, with at least 1 attack in the past 6 months.

Efficacy Endpoints

Primary efficacy endpoint:

- Number of HAE attacks per week from Day 8 to Day 50

Secondary efficacy endpoints:

- Number of HAE attacks per week from Day 1 to Day 50

- Number of HAE attacks per week from Day 8 to Day 64

- Number of HAE attacks per week from Day 8 to Day 92

Results

37 subjects were enrolled in the study; 13 placebo, 24 lanadelumab.

The mean age was 39.9 years and ranged from 18 to 71 years. 62% of the subjects were female. All treated subjects were white.
The baseline demographics in the treatment arms were acceptably balanced comparing placebo and total lanadelumab with the exception of gender (67% in the placebo group; 54% in the lanadelumab group). There was however poor balance between the different lanadelumab treatment arms in several parameters. The most prominent difference was seen in the number of HAE attacks which ranged from 7.0 attacks in the last 12 months in the lanadelumab 30 mg arm to 35.2 in the lanadelumab 400 mg arm (placebo 22.7; total lanadelumab 22.1). The difficulties to get the treatment arms balanced due to low number of subjects in each arm (N=4-11) is acknowledged.

The main objective of the study was to assess safety and tolerability.
The pre-specified, primary efficacy analysis was based on subjects in the 300 mg, 400 mg, and placebo dose groups with a historical baseline attack rate of at least 2 attacks over the last 3 months prior to enrolment. The primary efficacy endpoint was met (Table 5).

Table 5 Primary Efficacy Analysis: HAE Attack Rate per Week—Primary Efficacy Analysis Population (Day 8 to Day 50)

Parameter	DX-2930 300 mg (N=5)	DX-2930 400 mg (N=11)	DX-2930 Combined 300 and 400 mg (N=16)	Placebo (N=13)
n[a]	4	11	15	11
Baseline HAE attack rate (attacks/week), mean (SD)[b]	0.33 (0.246)	0.55 (0.174)	0.49 (0.211)	0.39 (0.177)
Overall HAE attack rate, unadjusted (attacks/week), mean (SD)[c]	0	0.048 (0.1504)	0.034 (0.1289)	0.364 (0.3638)
HAE attack rate GEE analysis[d]				
Estimated mean rate (attacks/week) (SE)	0	0.045 (0.0332)	0.033 (0.0240)	0.371 (0.0960)
P value (vs placebo)	< 0.0001	0.0050	0.0012	
% change in mean rate (vs placebo)	−100.0	−87.8	−91.1	
95% CI for % change	−100.0, −100.0	−97.2, −46.9	−97.9, −61.6	

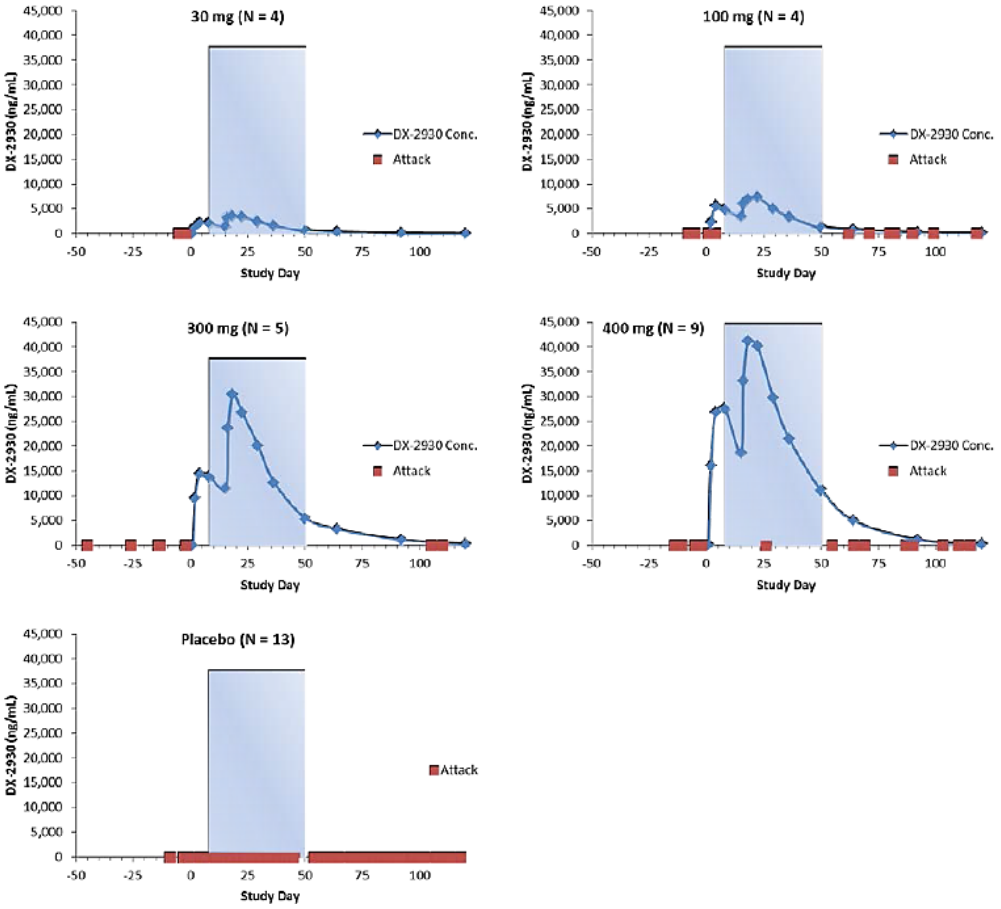
Source: Table 14.2.2.2.1.1
a Number of subjects included in analysis. Only subjects who had a baseline attack rate of at least 2 attacks in the last 3 months prior to enrolment are included.
b Baseline is defined as historical HAE attacks over the last 3 months from Day 1 prior to dosing.
c Weighted statistics, unadjusted for baseline attack rate.
d The result is based on GEE analysis of repeated counts per week during the observation period (Days 8 to 50). Baseline HAE attack rate per week is a covariate, treatment group is a fixed effect, and subject is a random effect in the GEE model with independence working correlation structure. The observed rate of HAE occurrence was 0% for the 300 mg treatment group and thus, an arbitrarily small value (0.000001) was imputed for the HAE occurrence variable for a random 300 mg subject at Week 2 to enable the GEE analyses to converge.

Secondary end points:

The secondary efficacy endpoints were met. From Day 1 to Day 50, Day 8 to Day 64, and Day 8 to Day 92, a 100% reduction versus placebo in the HAE attack rate (adjusted for the baseline attack rate) was observed for the 300 mg cohort ($p<0.0001$) during all 3 time periods and an 82% to 85% reduction versus placebo was observed for the 400 mg cohort during these 3 time periods ($p= 0.0141$, $p<0.0001$ and $p<0.0001$, respectively).

The beneficial effect of lanadelumab in prevention of HAE-attacks was further supported by a post hoc analysis comparing mean lanadelumab concentration with incidence of HAE attacks indicating a correlation between lanadelumab exposure and the number of attacks (Table 6).

Table 6 Angioedema Attack Incidence by Mean Lanadelumab Exposure- Pharmacodynamic Population (Study DX-2930-02)



Conclusion DX-2930-02

The efficacy results of study DX-2930-02 were considered a Proof-of-concept to assess the potential of lanadelumab as a prophylactic agent to prevent acute attacks in subjects with HAE. This is agreed.

2.5.2. Main study (DX-2930-03)

Title of study

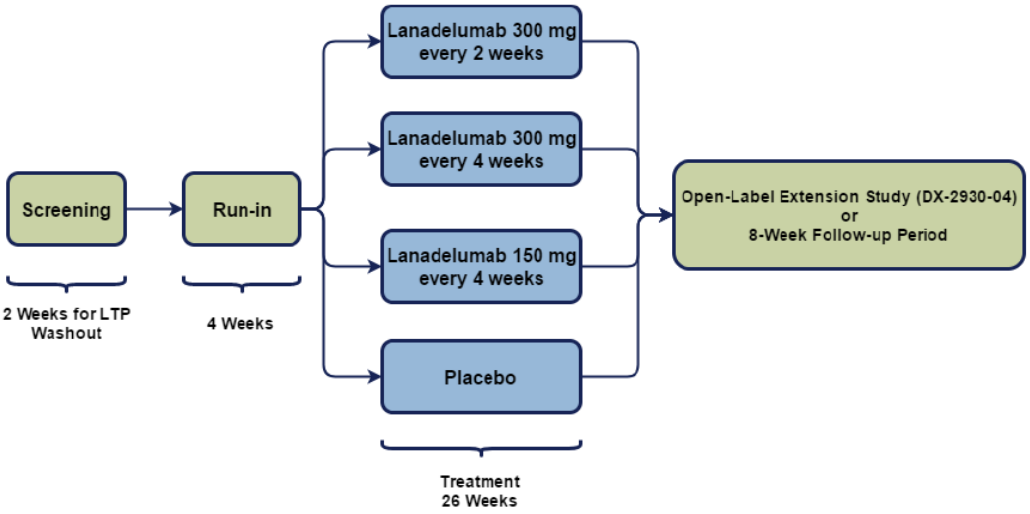
A Multicenter, Randomized, Double-Blind, Placebo-controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE) (Help study).

Methods

Study design

The outlines of study DX-2930-03 is summarised in Table 4 above.

Figure 4 Schematic Study Design for Study DX-2930-03



In study DX-2930-02, efficacy was shown with two doses, given 14 days apart, of lanadelumab of 300 mg and 400 mg. In order to evaluate if lower drug levels could be effective in preventing HAE attacks, three different dosing regimens (150 mg q4w, 300 mg q4w, 300 mg q2w), were used in this study.

Subjects were stratified by baseline attack rates (1 to <2 attacks per 4 weeks, 2 to <3 attacks per 4 weeks, and ≥3 attacks per 4 weeks) and randomised into 1 of 4 parallel treatment arms in a 3:2:2:2 ratio (placebo, lanadelumab 150 mg every 4 weeks [q4wks], lanadelumab 300 mg q4wks, or lanadelumab 300 mg q2wks by SC injection).

Study Participants

Main eligibility criteria

The main inclusion criteria were subjects ≥ 12 years of age with HAE type I or II and a baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.

Main exclusion criteria were

- Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE), HAE with normal C1-INH (also known as HAE Type III), idiopathic angioedema, or recurrent angioedema associated with urticaria.
- Exposure to angiotensin-converting enzyme (ACE) inhibitors or any oestrogen-containing medications with systemic absorption (such as oral contraceptives or hormonal replacement therapy) within 4 weeks prior to screening.
- Exposure to androgens within 2 weeks prior to entering the run-in period.
- Use of long-term prophylactic therapy for HAE within 2 weeks prior to entering the run-in period.
- Use of short-term prophylaxis for HAE within 7 days prior to entering the run-in period.
- Any of the following liver function test abnormalities: alanine aminotransferase (ALT) >3x upper limit of normal, or aspartate aminotransferase (AST) >3x upper limit of normal, or total bilirubin >2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).

- Pregnancy or breastfeeding

Treatments

This was a placebo-controlled study. Subjects were randomized to receive any one of the following dosing regimens by subcutaneous (SC) injection during 26 weeks:

- o lanadelumab 150 mg every 4 weeks (q4wks),
- o lanadelumab 300 mg q4wks,
- o lanadelumab 300 mg every 2 weeks (q2wks), or
- o placebo q2wks.

Lanadelumab is provided at a nominal concentration of 150 mg/ml solution. Placebo SC is administered to subjects randomized to the placebo arm and in between doses of lanadelumab for subjects randomized to the 300 mg or 150 mg q4wks treatment arms.

In order to maintain the blind, regardless of treatment assignment, all subjects were to receive 2 SC injections of blinded investigational or reference product administered in the same upper arm with at least 2 cm separation between each injection site every 2 weeks.

Objectives

Primary objective:

To evaluate the efficacy of lanadelumab in preventing HAE attacks

Secondary objective:

To evaluate the safety of repeated SC administrations of lanadelumab

Tertiary objectives:

- o To evaluate the PD effects of chronically administered lanadelumab
- o To assess the immunogenicity of chronically administered lanadelumab
- o To evaluate the PK of chronically administered lanadelumab
- o To evaluate the effect of lanadelumab on health-related quality of life (HRQoL).

Outcomes/endpoints

Primary Efficacy Endpoint

- Number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182).

Secondary Efficacy Endpoints (rank ordered)

- Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182).
- Number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182).

- Number of investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182.

Exploratory Efficacy Endpoints

- Time to first HAE attack after Day 14, i.e., the duration that a subject is attack-free after Day 14.
- Number of high-morbidity investigator-confirmed HAE attacks during the efficacy evaluation period; a high-morbidity HAE attack was defined as any attack that had at least one of the following characteristics: severe, resulted in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90 mm Hg, requires intravenous (IV) hydration, or associated with syncope or near-syncope) or laryngeal.

Sample size

Sample size calculation was based on simulations using unilateral testing at the 2.5%-level.

Randomisation

Randomization was performed using an Interactive Web-based Randomization System (IWRS). The trial used a double-bind approach. The applicant implemented procedures to help ensure double-blinding. There was a large difference in the number of HAE attacks between treatment groups, which may have been clinically perceivable by investigators. However, the primary endpoint collection relied on standardized guidelines, which may have helped limiting bias. Also, randomization was not stratified on centre, which somewhat reduces the possibility of deducing the treatment allocations.

Blinding (masking)

To maintain the blind to the q2wks treatment arm, subjects in the q4wks arms received placebo injection in between doses of lanadelumab.

Statistical methods

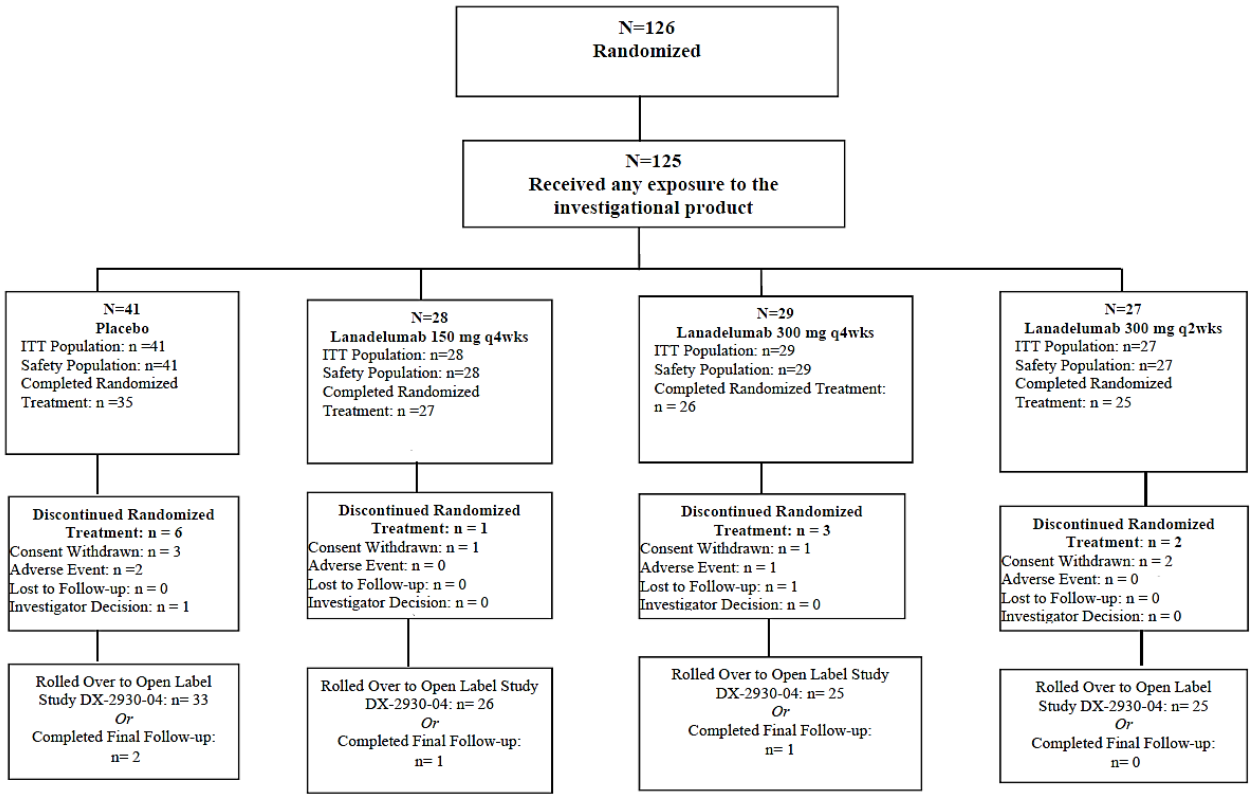
The primary efficacy endpoint was compared for each active treatment group (lanadelumab) to the placebo group using a Poisson regression model. The results were adjusted for baseline attack rate by including the normalized baseline attack rate as a fixed effect in the model. The logarithm of time in days each subject was observed during the treatment period was used as an offset variable, and a Pearson chi-square scaling of standard errors was used to account for potential over-dispersion. The statistical methods for study DX-2930-03 are generally considered acceptable.

Results

Participant flow

The subject disposition is summarised in Figure 5.

Figure 5 Overview of Subject Disposition



ITT= intent-to-treat population; N, n= number of subjects; SC= subcutaneous; q2wks=every 2 weeks; q4wks=every 4 weeks

Of note, only 27/125 patients received 300 mg q2w, which is the claimed dose regime.

One patient randomised to the 150 mg q4wks was excluded due to screening failure before treatment.

Recruitment

Date of study initiation: 03 March 2016

Date of study completion: 13 April 2017

Conduct of the study

In total, 9.6% of the subjects discontinued the study; 14.6% in the placebo arm and 7.1% in the lanadelumab arms. There was no obvious dose dependency in the discontinuation rates between the lanadelumab treatments arms; however, the absolute number of subjects discontinuing the study was very low (N=1-3) in the lanadelumab arms. The most common reason for discontinuation in both the placebo and lanadelumab arms was Consent withdrawn (placebo N=3; lanadelumab N=4) followed by Adverse event (placebo N=2; lanadelumab N=1)

One subject in the placebo group had measureable concentrations of lanadelumab in the same range as patients receiving a 300 mg dose. The Applicant considered that could either be due to contamination of the patients PK sample with lanadelumab or an inadvertent administration of lanadelumab to this subject, but neither theory could be proven in the investigation. No other misdosing was reported.

Other reported protocol violations are not considered to have affected the integrity of the study.

Baseline data

Table 7 Demography (ITT Population)

Characteristic	Placebo (N=41)	Lanadelumab				Total (N=125)
		150 mg q4Wks (N=28)	300 mg q4Wks (N=29)	300 mg q2Wks (N=27)	Total (N=84)	
Age (years)[a]						
n	41	28	29	27	84	125
Mean (SD)	40.1 (16.75)	43.4 (14.91)	39.5 (12.85)	40.3 (13.35)	41.0 (13.66)	40.7 (14.69)
Median (Min, Max)	42.4 (12, 70)	45.3 (16, 73)	40.7 (12, 59)	38.4 (15, 62)	42.7 (12, 73)	42.4 (12, 73)
Age Category (years)[a], n (%)[a]						
<18	4 (9.8)	1 (3.6)	3 (10.3)	2 (7.4)	6 (7.1)	10 (8.0)
≥65	2 (4.9)	3 (10.7)	0 (0.0)	0 (0.0)	3 (3.6)	5 (4.0)
Sex, n (%)						
Male	7 (17.1)	8 (28.6)	10 (34.5)	12 (44.4)	30 (35.7)	37 (29.6)
Female	34 (82.9)	20 (71.4)	19 (65.5)	15 (55.6)	54 (64.3)	88 (70.4)
Race, n (%)						
White	39 (95.1)	25 (89.3)	23 (79.3)	26 (96.3)	74 (88.1)	113 (90.4)
Black or African American	2 (4.9)	1 (3.6)	6 (20.7)	1 (3.7)	8 (9.5)	10 (8.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	2 (7.1)	0 (0.0)	0 (0.0)	2 (2.4)	2 (1.6)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)						
n	41	28	29	27	84	125
Mean (SD)	76.33 (22.669)	77.61 (15.638)	78.50 (16.575)	90.55 (25.150)	82.08 (20.123)	80.19 (21.075)
Median (Min, Max)	70.10 (36.7, 146.0)	76.80 (50.0, 116.0)	75.70 (46.8, 121.2)	86.60 (55.2, 150.0)	78.45 (46.8, 150.0)	75.50 (36.7, 150.0)
BMI (kg/m^2)[b]						
n	41	28	29	27	84	125
Mean (SD)	27.51 (7.737)	26.94 (4.666)	28.09 (5.158)	31.04 (7.807)	28.65 (6.173)	28.28 (6.717)
Median (Min, Max)	26.71 (16.8, 55.0)	26.10 (19.0, 38.8)	27.14 (18.3, 38.4)	28.09 (21.3, 47.6)	27.16 (18.3, 47.6)	27.14 (16.8, 55.0)

Subjects were included from 41 clinical sites in 6 countries: United States (N=86), Germany (N=18), Canada (N=7), Italy (N=6), United Kingdom (N=5) and Jordan (N=3). 29 subjects (23.2%) were included in Europe and 86 subjects (68.8%) in the US.

The proportion of male subjects was 17.1% in the placebo arm vs 35.7% in the lanadelumab arms, ranging from 28.6% in the 150 mg q4wks arm to 44.4% in the 300 mg q2wks arm. Randomization was stratified by the baseline attack rate observed during the run-in period but not by gender. The imbalance in gender between the treatment arms therefore indicates that there was no major correlation between gender and attack frequency;

however, there are publications indicating a more severe disease in women. This is further discussed below, as gender was one of the predefined subgroup analyses included in the statistical analysis plan for the primary endpoint.

The proportion of black/African American subjects was higher in the lanadelumab 300 mg q4wks arm than in the other treatment arms including placebo (20.7% vs 3.6-4.9%).

In total, 10 subjects <18 years (range 12-17 years) were included in the study; 6 in the lanadelumab arms and 4 in the placebo arm. Overweight or obese patients represented approximately 2/3 of the included patients.

Table 8 Baseline HAE Attack Characteristics -ITT Population

Characteristic	Placebo (N=41)	Lanadelumab				Total (N=125)
		150 mg q4Wks (N=28)	300 mg q4Wks (N=29)	300 mg q2Wks (N=27)	Total (N=84)	
Age at Onset of Angioedema Symptoms (years)						
Mean (SD)	11.2 (8.21)	12.0 (8.76)	14.6 (11.16)	15.0 (8.67)	13.8 (9.61)	13.0 (9.22)
Median (Min, Max)	8.0 (2, 41)	10.5 (1, 40)	12.0 (1, 49)	14.0 (2, 43)	12.5 (1, 49)	12.0 (1, 49)
HAE Type, n (%)						
Type I	38 (92.7)	25 (89.3)	27 (93.1)	23 (85.2)	75 (89.3)	113 (90.4)
Type II	3 (7.3)	3 (10.7)	2 (6.9)	4 (14.8)	9 (10.7)	12 (9.6)
History of Laryngeal Attacks, n (%)						
Yes	27 (65.9)	17 (60.7)	17 (58.6)	20 (74.1)	54 (64.3)	81 (64.8)
No	14 (34.1)	11 (39.3)	12 (41.4)	7 (25.9)	30 (35.7)	44 (35.2)
Primary Attack Locations (Combined)[a], n (%)						
Laryngeal	10 (24.4)	3 (10.7)	6 (20.7)	5 (18.5)	14 (16.7)	24 (19.2)
Abdominal	35 (85.4)	20 (71.4)	27 (93.1)	21 (77.8)	68 (81.0)	103 (82.4)
Peripheral	30 (73.2)	25 (89.3)	22 (75.9)	23 (85.2)	70 (83.3)	100 (80.0)
Number of Attacks in the Last Month						
Mean (SD)	4.15 (3.978)	4.61 (5.953)	3.76 (3.512)	2.96 (2.794)	3.79 (4.310)	3.90 (4.192)
Median (Min, Max)	3.00 (0.0, 15.0)	3.00 (0.0, 30.0)	2.00 (0.0, 14.0)	2.00 (0.0, 12.0)	3.00 (0.0,30.0)	3.00 (0.0, 30.0)
Number of Attacks in the Last 12 Months						
Mean (SD)	45.46 (43.441)	47.07 (68.607)	37.07 (35.516)	22.15 (18.172)	35.61 (46.520)	38.84 (45.595)
Median (Min, Max)	30.00 (0.0, 185.0)	34.00 (2.0, 365.0)	24.00 (1.0, 140.0)	20.00 (0.0, 72.0)	24.00 (0.0, 365.0)	24.00 (0.0, 365.0)
Run-in HAE Attack Rate (attacks/month)[b]						
Mean (SD)	4.02 (3.265)	3.22 (1.830)	3.71 (2.507)	3.52 (2.327)	3.48 (2.225)	3.66 (2.611)
Median (Min, Max)	3.00 (1.0, 14.7)	3.18 (1.0, 6.7)	3.00 (1.0, 10.5)	3.11 (1.0, 9.0)	3.00 (1.0, 10.5)	3.00 (1.0, 14.7)

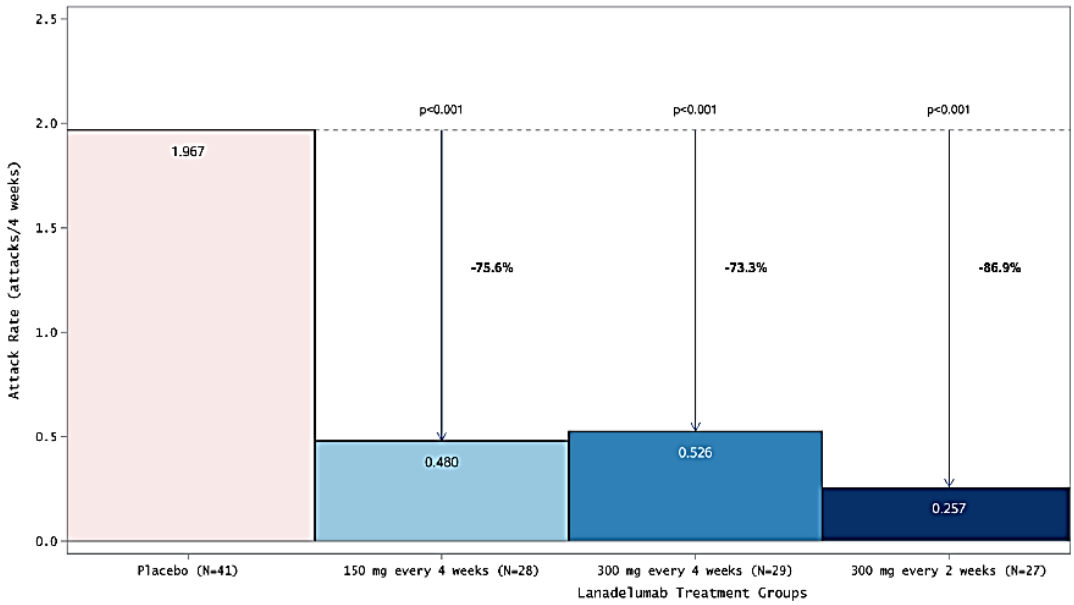
a Subjects may be counted in more than one category.
b Run-in HAE attack rate is calculated as the number of HAE attacks occurring during the run-in period divided by the number of days the subject contributed to the run-in period multiplied by 28 days. A month is defined as 28 days.
Source: Table 14.1.4.1; Listing 16.2.4.2

In spite of stratification by the baseline attack rate observed during the run-in period, the rate of HAE attacks during run-in was not fully balanced and the standard deviations [SD] were large. This could be due to the highest stratum being indefinitely large (≥3 attacks/4 weeks). Nevertheless, the imbalance may have impact on the robustness of the data. The issue is further discussed below.

Outcomes and estimation

The primary efficacy endpoint was the number of investigator confirmed HAE attacks during the treatment period given as number of attacks/4 weeks.

Figure 6 Poisson Regression of Investigator-Confirmed HAE Attacks During the Treatment Period (Day 0 to Day 182) by Treatment Group-ITT Population



The primary endpoint of the study was met, as the number of investigator confirmed HAE attacks during the treatment period was reduced in all lanadelumab treatment arms compared to placebo. The relative risk reduction ranged from 73% in the 300 mg q4wks to 87% in the 300 mg q2wks compared to placebo, corresponding to a mean decrease of approximately 1.5 attack/4 weeks in the 150 mg q4wks and 300 mg q4wks arms and 1.75 attacks/4 weeks in the 300 mg q2wks treatment arm.

For *Age <18 years*, the reduction in mean HAE attack rate was (0.30 [SD=0.263] and 0.31 [0.433]) in 300 mg q4wks and 300 mg q2wks compared to placebo (0.92 [0.992]).

As discussed above, the run-in HAE attack rate was not fully balanced between treatment arms. The primary efficacy analysis was a Poisson model, with in HAE attack rate during the baseline (run-in) period included as a covariate.

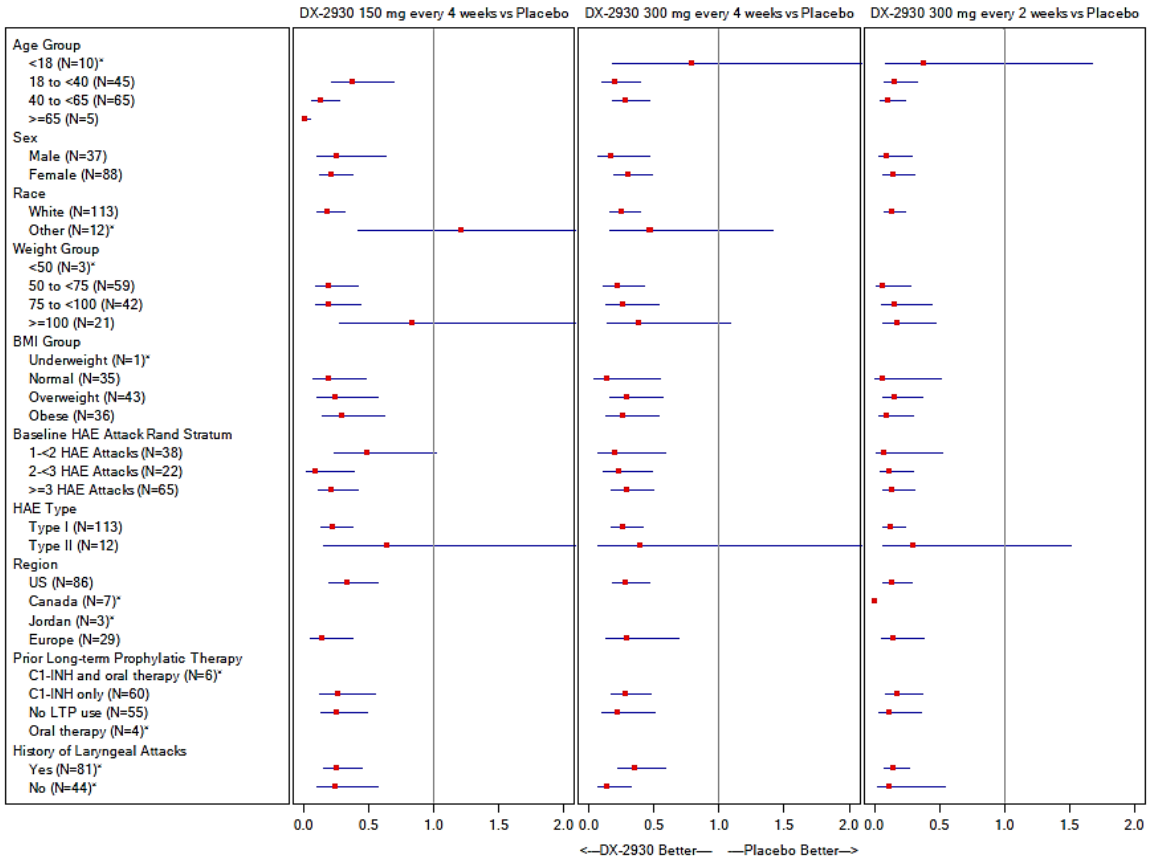
Further CHMP request, the applicant has provided an overview on the effect of baseline attack rate on attack rate during the trial, including a subgroup analysis on HAE attack rate (primary endpoint) based on run-in period HAE attack rate. Data provided confirm that the treatment period attack rate was strongly influenced by the baseline attack rate (higher the run-in period attack rate, the higher the treatment period attack rate). In all subgroups, the decrease in HAE attack rate was larger in the lanadelumab treatment arms compared to placebo.

These changes were statistically significant at the 0.05 level, with the exception of 150 mg every 4 weeks in the subgroup Run-in HAE attack rate 1-<2 attacks/month (p=0.055).

Furthermore, the applicant has provided data on the absolute change from baseline in each treatment arm for the primary and secondary endpoints. For all endpoints, the change from baseline was 38-40% in the placebo arm and 84-86%, 84-97% and 88-92% for lanadelumab 150 mg q4w, 300 mg q4w and 300 mg q2w, respectively.

For the primary endpoint, pre-specified subgroup analyses were performed (Figure 7).

Figure 7 Forest Plot of Rate Ratio on Number of Investigator-Confirmed HAE Attacks by Subject Subgroups-ITT Population

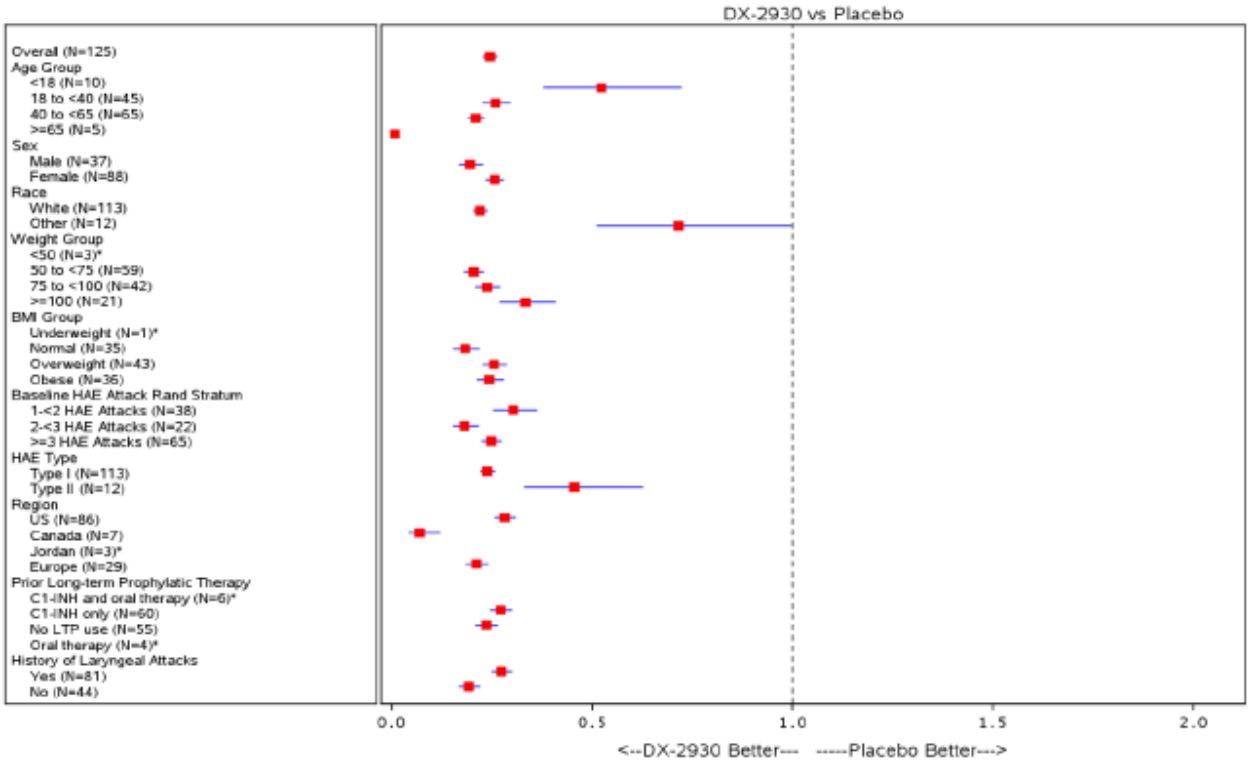


Results from subgroup analyses were generally consistent with the results from the entire population with a few exceptions (*Age <18 years*, *HAE type II, weight ≥100 mg* [except in the 300 mg q4wks arm] and *Other race than white)*. However, in all subgroups other than *Other race than white* treatment arm 150 mg q4wks, the point estimate favours lanadelumab treatment, though the confidence interval covers 1.

For some subgroups, including *Age <18 years*, *HAE type II* and *Other race than white*, the number of subjects is low (N=10-12 in total for all lanadelumab dosing regimens and placebo). It is acknowledged that the number of subjects in these subgroups may be too low to detect a difference between lanadelumab and placebo. In order to get a clearer view of potential differences between subgroups and the entire population, the Applicant was asked to present a Forest plot of rate ratio on number of investigator-confirmed HAE attacks by each subgroup for the ITT population with pooled data from the three lanadelumab treatment arms compared to placebo. In

this ad hoc pooled analysis, the point estimate favours lanadelumab treatment for all subject subgroups with an adequate number of subjects. The confidence interval does not cover 1 in any subgroup (Figure 8).

Figure 8 Forest Plot of Rate Ratio on Number of Investigator-Confirmed HAE Attacks by Subject Subgroups



Pharmacokinetic analyses suggest a lower exposure in subjects with higher body weight as discussed earlier. Moreover, in analysing the impact of baseline covariates on the time to first attack in study DX-2930-04, it was observed that at any given time subjects with BMI classified as overweight or obese have an increased probability of having an attack compared with normal BMI subjects. Using PK/PD data, the Applicant has clarified that the 300 mg q2wks dosing was associated with lanadelumab exposure approximate or above the IC_{90} of PD and $EAUC_{90}$ for efficacy in patients across a large range of body weight (46.8-150 kg). The Applicant has also provided an ad hoc subgroup analysis based on baseline weight.

Table 9 Number of Investigator-Confirmed HAE Attack by Weight and Treatment Group in Treatment Period in Study DX-2930-03-ITT Population

Weight group 50 to <75 kg (N=59)				
	Placebo (N=24)	**Lanadelumab 150 mg q4wks (N=12)**	**Lanadelumab 300 mg q4wks (N=13)**	**Lanadelumab 300 mg q2wks (N=10)**
Baseline attack rate, mean (SD)	3.79 (2.29)	2.58 (1.43)	2.70 (1.89)	2.60 (2.18)
Treatment period HAE attack rate, mean (SD)	2.41 (1.76)	0.33 (0.60)	0.39 (0.39)	0.24 (0.52)
LS Mean (95% CI) monthly attack rate	1.79 (1.41, 2.27)	0.35 (0.17, 0.72)	0.39 (0.21, 0.73)	0.12 (0.03, 0.48)
% Reduction in mean attack rate relative to placebo (95% CI)		80% (58.13, 90.69)	78% (57.89, 88.93)	93% (72.51, 98.29)
Weight group 75 to <100kg (N=42)				
	Placebo (N=9)	**Lanadelumab 150 mg q4wks (N=14)**	**Lanadelumab 300 mg q4wks (N=11)**	**Lanadelumab 300 mg q2wks (N=8)**
Baseline attack rate, mean (SD)	5.51 (5.32)	3.39 (1.93)	4.97 (2.83)	4.32 (2.06)
Treatment period HAE attack rate, mean (SD)	3.69 (2.96)	0.48 (0.55)	0.88 (1.18)	0.44 (0.62)
LS Mean (95% CI) monthly attack rate	2.69 (1.78, 4.07)	0.53 (0.27, 1.05)	0.70 (0.38, 1.30)	0.43 (0.17, 1.10)
% Reduction in mean attack rate relative to placebo (95% CI)		80% (55.97, 91.17,)	74% (46.80, 87.26)	84% (55.78, 94.22)
Weight group ≥100kg (N=21)				
	Placebo (N=6)	**Lanadelumab 150 mg q4wks (N=2)**	**Lanadelumab 300 mg q4wks (N=4)**	**Lanadelumab 300 mg q2wks (N=9)**
Baseline attack rate, mean (SD)	3.72 (2.82)	5.85 (0.73)	4.23 (2.15)	3.83 (2.60)
Treatment period HAE attack rate, mean (SD)	1.54 (0.76)	1.45 (0.75)	0.60 (0.49)	0.27 (0.40)
LS Mean (95% CI) monthly attack rate	1.57 (0.99, 2.49)	1.32 (0.49, 3.53)	0.61 (0.24, 1.53)	0.27 (0.11, 0.66)
% Reduction in mean attack rate relative to placebo (95% CI)		16% (-151.41, 72.01)	61% (-8.45, 86.17	83% (52.91, 93.65)

CI= confidence interval; HAE= hereditary angioedema; ITT=intent-to-treat; LS=least squares; q2wk=every 2 weeks; q4wk=every 4 weeks; SD=standard deviation

Note: The number of subjects or the observed events was too small in <50 kg weight category to support any inferential conclusion (300 mg q4wks: N=1 and placebo arm: N=2).

Run-in period in Study DX-2930-03=baseline for subjects in the study.

Attack rate=attacks/month; A month is defined as a 4 week period or 28 days.

Source: Module 5.3.5.1, Study DX-2930-03 CSR, Table 14.2.2.10

Effect on HAE attack rate of 300 mg q2w was shown in all weight subgroups, including subjects >100 kg. On the contrary, the dose regimen 150 mg q4w did not exert any effect on HAE attack rate in subjects >100 kg. It should be noted that due to the relatively small study, the number of subjects in each subgroup is low. However, the number of subjects in the >100 kg subgroup was comparable to the other weight subgroups. Moreover, it is noted that there were no treatment differences regarding gender, which is reassuring considering the imbalances in gender between the treatment arms discussed above.

Study DX-2930-03 met its three secondary efficacy endpoints (Table 10).

Table 10 Primary and Rank Ordered Secondary Efficacy Endpoints-ITT Population

Endpoint Statistic	Placebo (N=41)	Lanadelumab 150mg q4wks (N=28)	Lanadelumab 300 mg q4wks (N=29)	Lanadelumab 300 mg q2wks (N=27)
Number of investigator-confirmed HAE attacks from Day 0 to 182[a]				
Model-based treatment period HAE attack rate (attacks/4 weeks)[b]				
LS Mean (95% CI)	1.967 (1.640, 2.358)	0.480 (0.313, 0.735)	0.526 (0.358, 0.771)	0.257 (0.145, 0.458)
% Change mean attack rate (vs placebo)[c]		**-75.609**	**-73.271**	**-86.921**
% Change 95% CI		(-84.650, -61.243)	(-82.379, -59.456)	(-92.828, -76.150)
Adjusted p-values[d]		<0.001	<0.001	<0.001
Number of Investigator-Confirmed HAE Attacks requiring Acute Treatment from Day 0-182 (1st Rank)				
Model-based treatment period HAE attack rate (attacks/4 weeks)[b]				
LS Mean (95% CI)	1.637 (1.337, 2.005)	0.314 (0.184, 0.535)	0.423 (0.276, 0.648)	0.208 (0.109, 0.396)
% Change mean attack rate (vs placebo)[c]		**-80.842**	**-74.169**	**-87.299**
% Change 95% CI		(-89.169, -66.114)	(-83.733, -58.983)	(-93.494, -75.204)
Adjusted p-values[d]		<0.001	<0.001	<0.001
Number of Moderate or Severe Investigator-Confirmed HAE Attacks from Day 0-182 (2nd Rank)				
Model-based treatment period HAE attack rate (attacks/4 weeks)[b]				
LS Mean (95% CI)	1.216 (0.971, 1.522)	0.359 (0.221, 0.581)	0.325 (0.199, 0.529)	0.202 (0.106, 0.386)
% Change mean attack rate (vs placebo)[c]		**-70.497**	**-73.285**	**-83.394**
% Change 95% CI		(-82.696, -49.699)	(-84.316, -54.496)	(-91.618, -67.099)
Adjusted p-values[d]		<0.001	<0.001	<0.001
Number of Investigator-Confirmed HAE Attacks from Day 14-182 (3rd Rank)				
Model-based treatment period HAE attack rate (attacks/4 weeks)[b]				
LS Mean (95% CI)	1.988 (1.652, 2.391)	0.445 (0.283, 0.698)	0.489 (0.326, 0.734)	0.218 (0.115, 0.414)
% Change mean attack rate (vs placebo)[c]		**-77.622**	**-75.377**	**-89.008**
% Change 95% CI		(-86.253, -63.572)	(-84.115, -61.833)	(-94.325, -78.707)
Adjusted p-values[d]		<0.001	<0.001	<0.001

In the exploratory analyses, the results from the primary and secondary endpoints were supported.

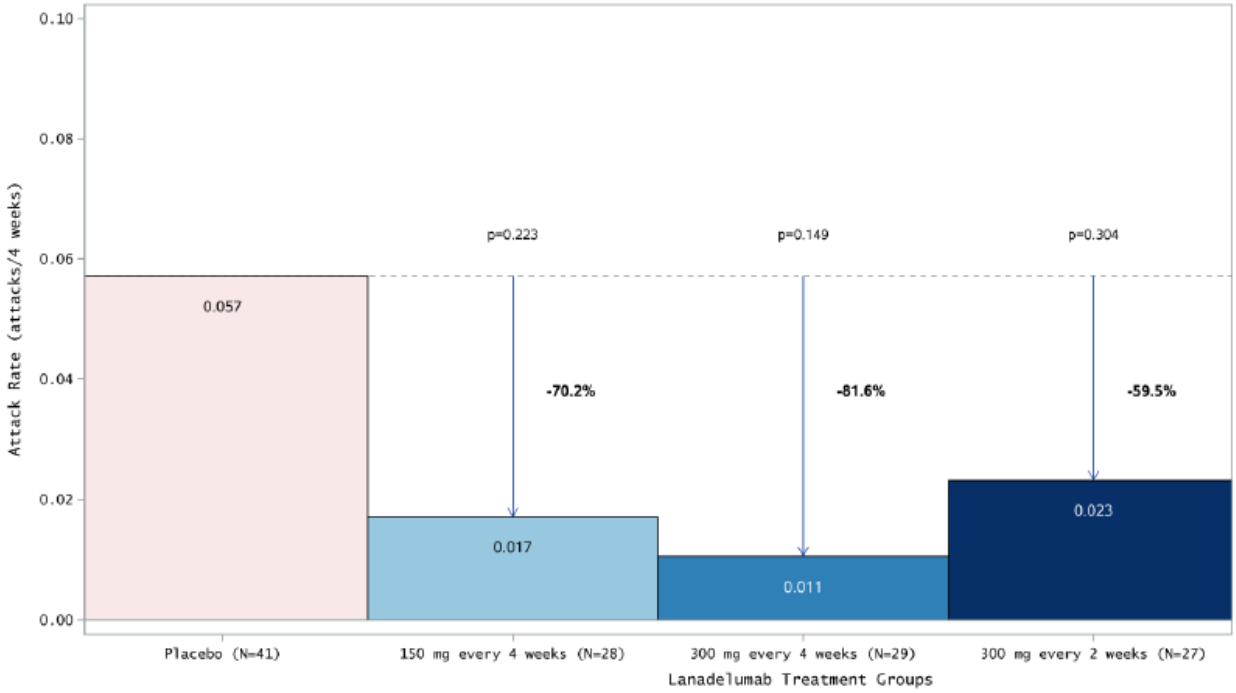
The *time to first attack* after Day 0, Day 14, Day 28, and Day 70 was significantly longer for the lanadelumab treated subjects compared to the placebo treated subjects (unadjusted p<0.001 for all 3 lanadelumab treatment arms) regardless of the run-in-period HAE attack rate.

The percentage reduction in the *incidence of high morbidity investigator-confirmed HAE attacks* during the treatment period compared to placebo was statistically significant for all 3 lanadelumab treatment arms: 79.2% in 150 mg q4wks arm, 86.3% in 300 mg q4wks arm, and 84.7% in 300 mg q2wks arm.

Overall, the number of subjects who had *investigator-confirmed HAE attacks resulting in an emergency department visit or resulting in admission to the hospital* was too low in each treatment arm for statistical comparison with placebo.

The percentage reduction in the *investigator-confirmed laryngeal HAE attack rate* ranged from 59.5% to 81.6% in the lanadelumab treatment arms compared to placebo. The number of subjects who had investigator-confirmed laryngeal HAE attacks was too low in each treatment arm for a statistically significant comparison with placebo.

Table 11 Poisson Regression of Investigator-Confirmed Laryngeal HAE Attacks during the Treatment Period (Day 0 to Day 182) by Treatment Group -ITT Population



HAE= hereditary angioedema; ITT= intent-to-treat

Note: Unadjusted p-values.

Source: Table 14.2.11.1; Figure 2539.7

The Responder analysis of reduction from run-in period in the investigator-confirmed HAE attack rate is shown in Table 12.

Table 12 Responder Analysis Comparing Investigator-Confirmed HAE Attacks During the Treatment Period (Day 0 to Day 182) by Responder Threshold and Treatment Group -ITT Population

Criteria	Placebo (N=41) n (%)	Lanadelumab		
		150 mg q4wks (N=28) n (%)	300 mg q4wks (N=29) n (%)	300 mg q2wks (N=27) n (%)
≥50% Reduction	13 (31.7)	25 (89.3)	29 (100.0)	27 (100.0)
≥60% Reduction	9 (22.0)	24 (85.7)	26 (89.7)	27 (100.0)
≥70% Reduction	4 (9.8)	22 (78.6)	22 (75.9)	24 (88.9)
≥80% Reduction	3 (7.3)	22 (78.6)	17 (58.6	22 (81.5)
≥90% Reduction	2 (4.9)	18 (64.3)	16 (55.2)	18 (66.7)
100% Reduction	1 (2.4)	11 (39.3)	9 (31.0)	12 (44.4)

Note: For each subject, the percentage reduction was calculated as the run-in period attack rate minus the treatment period attack rate divided by the run-in period attack rate, multiplied by 100. The percentage reduction groups are not mutually exclusive, subjects may appear in more than one group as applicable based on their percentage reduction.
Source: Table 14.2.12.1 and Table 14.2.13.1

The *use of rescue medications* in the lanadelumab treatment arms was lower compared to placebo during the treatment period.

Table 13 Rescue Medication Use During the Run-in Period and Treatment Period (Day 0 to Day 182)-ITT Population

Period Characteristics	Placebo N=41 n (%) m	Lanadelumab		
		150 mg q4wks (N=28) n (%) m	300 mg q4wks (N=29) n (%) m	300 mg q2wks (N=27) n (%) m
Run-in Period				
HAE Attacks - n (%) m	41 (100.0) 127	28 (100.0) 81	29 (100.0) 77	27 (100.0) 78
Rescue Medication Use - n (%) m				
Ecallantide	2 (4.9)2	3 (10.7)5	6 (20.7)8	1 (3.7) 3
Icatibant	22 (53.7) 38	13 (46.4) 28	13 (44.8) 41	13 (48.1)32
Nano-filtered or plasma-derived C1-INH	22 (53.7) 77	12 (42.9) 32	14 (48.3) 28	12 (44.4) 34
Recombinant C1-INH	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	1 (3.7) 2
Fresh frozen plasma	1 (2.4) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Treatment Period				
HAE Attacks - n (%) m	40 (97.6) 572	17 (60.7) 84	20 (69.0) 105	15 (55.6) 46
Rescue Medication Use - n (%) m				
Ecallantide	5 (12.2) 12	1 (3.6) 1	6 (20.7)18	0 (0.0) 0
Icatibant	27 (65.9) 172	9 (32.1) 25	11 (37.9) 69	10 (37.0) 20
Nano-filtered or plasma-derived C1-INH	27 (65.9) 362	7 (25.0) 31	4 (13.8) 7	6 (22.2) 26
Recombinant C1-INH	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0
Fresh frozen plasma	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

n=number of subjects experiencing the event; m=number of events

Subjects treated with lanadelumab demonstrated improvement in health-related quality of life (Table 14)

Table 14 ANCOVA results for change in AE-QoL scores from Day 0 to Day 182 by treatment arm, adjusted for baseline scores (ITT Population)

Treatment arm	AE-QoL Least Square Mean Change (SD)				
	Total	Functioning	Fatigue/ Mood	Fear/ Shame	Nutrition
Placebo	-4.72 (18.75)	-5.42 (22.72)	-1.79 (23.25)	-9 (24.02)	0.51 (22.5)
Lanadelumab 150 mg q4wks	-19.82 (19.07)#	-27.76 (23.12)#	-9.33 (23.62)	-22.53 (24.38)	-19.82 (22.76)#
Lanadelumab 300 mg q4wks	-17.38 (18.67)#	-24.29 (22.66)#	-13.86 (23.22)	-16.3 (23.71)	-13.34 (22.32)
Lanadelumab 300 mg q2wks	-21.29 (18.35)#	-35.97 (22.29)#	-15.78 (22.79)	-17.59 (23.29)	-18.03 (22.01)#
F and p-value	6.97***	12.23***	2.95*	3.8**	3.86**
Lanadelumab Total vs. Placebo: Least Square Mean Change (SD)					
Placebo	-4.71 (18.64)	-5.41 (22.92)	-1.79 (23.17)	-9.05 (23.92)	0.49 (22.43)
Lanadelumab Total	-19.47 (18.59)	-29.28 (22.88)	-13 (23.12)	-18.75 (23.74)	-17.01 (22.33)
F and p-value	20.67***	32.7***	7.82**	9.27***	10.68***

Notes: For ANCOVAs: p-value ***<0.01, **0.01- <0.04, *0.04<0.05, - ≥0.05; For post-hoc comparisons: p-value *<0.05
#: Significant differences between treatment and placebo arms on post-hoc pairwise comparison tests (Tukey-Kramer; p<0.05).
Source data: Table 3.3 from patient reported outcome report number 0238.0418.1.

Subjects who experienced 3 or more investigator-confirmed attacks before the end of the 4 weeks run-in period were allowed to exit the run-in period early and proceed to enrolment and randomisation. The proportion of patients exiting the run-in period in advance was comparable across randomization arms (~40% randomized subjects in each arm) (Table 15).

Table 15 Number of Patients who Exited Earlier the Run-in period in Each Treatment Arm by Baseline HAE Attack Rate Group-ITT Population- Study DX-2930-03

	Run-in period HAE attack rate (attacks/month)				
Treatment	1-<2 HAE Attacks	2-<3 HAE Attacks	≥3 HAE Attacks 'Non-escape'[a]	≥3 HAE Attacks 'Escape'[b]	Total
	Subject exited n (%)	Subject exited n (%)	Subject exited n (%)	Subject exited n (%)	N
Placebo	12 (29.2)	8 (19.5)	4 (9.7)	17 (41.4)	41
Lanadelumab 150 mg q4wks	10 (35.7)	3 (10.7)	4 (14.2)	11 (39.2)	28
Lanadelumab 300 mg q4wks	9 (31.0)	5 (17.2)	3 (10.3)	12 (41.3)	29
Lanadelumab 300 mg q2wks	7 (25.9)	6 (22.2)	3 (11.1)	11 (40.7)	27

HAE=hereditary angioedema; q2wks= every 2 weeks; q4wks=every 4 weeks

Note: Month is defined as a 4 weeks period or 28 days

[a] Baseline HAE attack rate group '≥3 HAE attacks non-escape' is the subgroup of subjects of ≥3 HAE attacks with run-in period duration ≥28 days.

[b] Baseline HAE attack rate group '≥3 HAE attacks escape' is the subgroup of subjects of ≥3 HAE attacks with run-in period duration <28 days.

Sources: Module 5.3.5.1 Study DX-2930-03 CSR Table r2613.1; Study DX-2930-03 Table r2729.1, Table r2729.2, Table r2729.3

Summary of main efficacy results

The following table summarises the efficacy results from the pivotal study DX-2930-03 supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16 Summary of efficacy for trial DX-2930-03

Title: HELP Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE)		
Study identifier	DX-2930-03	
Design	Multicentre, randomized, double-blind, placebo-controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks 4 weeks not applicable (inclusion in Open-label extension Study DX-2930-04 possible)
Hypothesis	Superiority vs placebo	
Treatments groups	Placebo	SC injection every second week for 26 weeks N= 41

	Lanadelumab 150 mg q4wks	Placebo SC injection every second week; lanadelumab 150 mg SC every second week for 26 weeks N=28
	Lanadelumab 300 mg q4wks	Placebo SC injection every second week; lanadelumab 300 mg SC every second week for 26 weeks N=29
	Lanadelumab 300 mg q2wks	Lanadelumab 300 mg SC every second week for 26 weeks N=27

Endpoints and definitions	Primary endpoint	Number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182).
	Secondary endpoints (rank ordered)	Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182). Number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182). Number of investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182).
Database lock	13 April 2017	

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat Analysis Day 182				
Descriptive statistics and estimate variability	Treatment group	Placebo	Lana 150 q4w	Lana 300 q4w	Lana 300 q2w
	Number of subject	41	28	29	27
	HAE attacks/4 weeks Day 0-180 LS mean (95% CI)	1.97 (1.64, 2.36)	0.48 (0.31, 0.74)	0.53 (0.36, 0.77)	0.26 (0.14, 0.46)

Effect estimate per comparison	Primary endpoint	Comparison groups	Lanadelumab 150 mg q4w vs placebo
		% Change mean attack rate (vs placebo)	-75.61
		% Change 95% CI	-84.65, -61.24
		Adjusted P-value	<0.001

		Comparison groups	Lanadelumab 300 mg q4w vs placebo		
		% Change mean attack rate (vs placebo)	-73.27		
		% Change 95% CI	-82.78, -59.46		
		Adjusted P-value	<0.001		
		Comparison groups	Lanadelumab 300 mg q2w vs placebo		
		% Change mean attack rate (vs placebo)	-86.92		
		% Change 95% CI	-92.83, -76.15		
		Adjusted P-value	<0.001		
Analysis description	**Secondary analyses**				
Analysis population and time point description	Intent to treat Analysis Day 182				
Descriptive statistics and estimate variability	Treatment group	Placebo	Lana 150 q4w	Lana 300 q4w	Lana 300 q2w
	Number of subject	41	28	29	27
	Number of HAE Attacks requiring Acute Treatment Day 0-182 LS mean (95% CI)	1.64 (1.34, 2.04)	0.31 (0.18, 0.54)	0.42 (0.28, 0.65)	0.21 (0.11, 0.40)
	Number of Moderate or Severe HAE Attacks Day 0-182 LS mean (95% CI)	1.22 (0.97, 1.52)	0.360 (0.22, 0.58)	0.32 (0.20, 0.53)	0.20 (0.11, 0.39)
	Number of HAE Attacks Day 14-182 LS mean (95% CI)	1.99 (1.65, 2.39)	0.44 (0.28, 0.70)	0.49 (0.33, 0.73)	0.22 (0.12, 0.41)
Effect estimate per comparison	Number of HAE Attacks requiring	Comparison groups	Lanadelumab 150 mg q4w vs placebo		
		% Change mean attack rate (vs placebo)	-80.84		

	Acute Treatment Day 0-182	% Change 95% CI	-89.17, -66.11
		Adjusted P-value	<0.001
		Comparison groups	Lanadelumab 300 mg q4w vs placebo
		% Change mean attack rate (vs placebo)	-74.17
		% Change 95% CI	-83.73, -58.98
		Adjusted P-value	<0.001
		Comparison groups	Lanadelumab 300 mg q2w vs placebo
		% Change mean attack rate (vs placebo)	-87.30
		% Change 95% CI	-93.49, -75.20
		Adjusted P-value	<0.001
	Number of Moderate or Severe HAE Attacks Day 0-182	Comparison groups	Lanadelumab 150 mg q4w vs placebo
		% Change mean attack rate (vs placebo)	-70.50
		% Change 95% CI	-82.70, -49.70
		Adjusted P-value	<0.001
		Comparison groups	Lanadelumab 300 mg q4w vs placebo
		% Change mean attack rate (vs placebo)	-73.28
		% Change 95% CI	-84.32, -54.50
		Adjusted P-value	<0.001
		Comparison groups	Lanadelumab 300 mg q2w vs placebo
		% Change mean attack rate (vs placebo)	-83.39
		% Change 95% CI	-91.62, -67.10
		Adjusted P-value	<0.001
	Number of HAE Attacks Day 14-182	Comparison groups	Lanadelumab 150 mg q4w vs placebo
		% Change mean attack rate (vs placebo)	-77.62
		% Change 95% CI	-86.25, -63.57
		Adjusted P-value	<0.001
		Comparison groups	Lanadelumab 300 mg q4w vs placebo
		% Change mean attack rate (vs placebo)	-75.38

		% Change 95% CI	-84.12, -61.83
		Adjusted P-value	<0.001
		Comparison groups	Lanadelumab 300 mg q2w vs placebo
		% Change mean attack rate (vs placebo)	-89.01
		% Change 95% CI	-94.32, -78.71
		Adjusted P-value	<0.001

Analysis performed across trials (pooled analyses AND meta-analysis)

Data from the Phase 3 studies have not been pooled by the applicant due to differences in study designs (e.g., placebo-controlled versus open-label) and the endpoints analysed. Efficacy results and results in sub-populations across Phase 3 studies have been compared by the applicant.

Description of number of attack rates in rollover (from Study DX-2930-03) patients in study DX-2930-04 yielded mean attack rates that seemed smaller in study DX-2930-04, compared to study DX-2930-03, regardless of the DX-2930-03 randomization arm, whichever the endpoint (investigator confirmed attack, attack requiring acute treatment, moderate-to-severe attack, high morbidity attack): rollover patients from the placebo arm seemed to benefit from switching to active treatment. Mean rates in rollover patients initially from the 300 mg q4wks and 150 mg q4wks arms seemed also lower in study DX-2930-04 (under dosage 300mg q2wks), but also in rollover patients initially from the 300 mg q2wks arm.

Clinical studies in special populations

No studies in special population have been performed.

Of note, 9 patients aged ≥65 years were included in the lanadelumab clinical studies. None of those were ≥85 years old (Table 17).

Table 17 Number of Subjects ⩾65 Years of Age who Participated in Lanadelumab Clinical Studies

Study Type	Study Cohort	Age (Years)		
		65 to <75 n/N (%)	75 to <85 n/N (%)	≥85 n/N (%)
Controlled Trials	DX-2930-01	0/32 (0.00)	0/32 (0.00)	0/32 (0.00)
	DX-2930-02	0/19 (0.00)	0/19 (0.00)	0/19 (0.00)
	DX-2930-03	5/125 (4.00)	0/125 (0.00)	0/125 (0.00)
	All controlled trials	5/176 (2.84)	0/176 (0.00)	0/176 (0.00)
Non Controlled Trials	DX-2930-04	10/212 (4.72)	1/212 (0.47)	0/212 (0.00)
	Nonrollover subjects	4/103 (3.88)	1/103 (0.97)	0/103 (0.00)
	Nonrollover former Study DX-2930-02 subjects	1/19 (5.26)	0/19 (0.00)	0/19 (0.00)
	Rollover subjects	6/109 (5.50)	0/109 (0.00)	0/109 (0.00)
Overall Trials	Unique subjects*	8/260 (3.08)	1/260 (0.38)	0/260 (0.00)

Supportive study (DX-2930-04)

Study title:

An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) (HELP Study ExtensionTM).

Study design:

Study DX-2930-04 was an open-label, long-term safety and efficacy extension study to DX-2930-03. Two types of subjects were enrolled into this study: rollovers from Study DX-2930-03 and non-rollovers (i.e., were not participants in Study DX-2930-03) . The treatment period was extended to 30 months in Amendment 3. A description of the final study design after Amendment 3 is provided.

Figure 9 Schematic study design

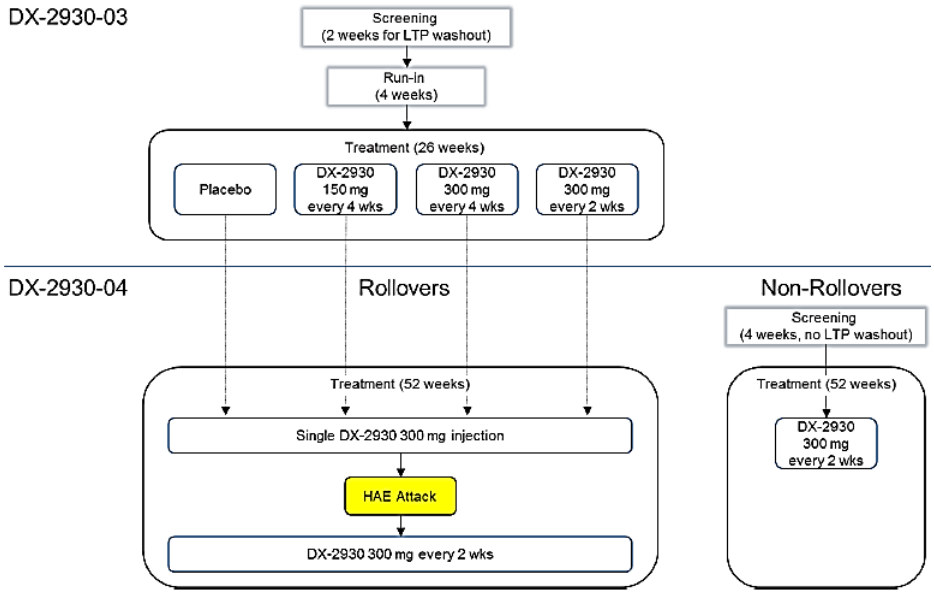
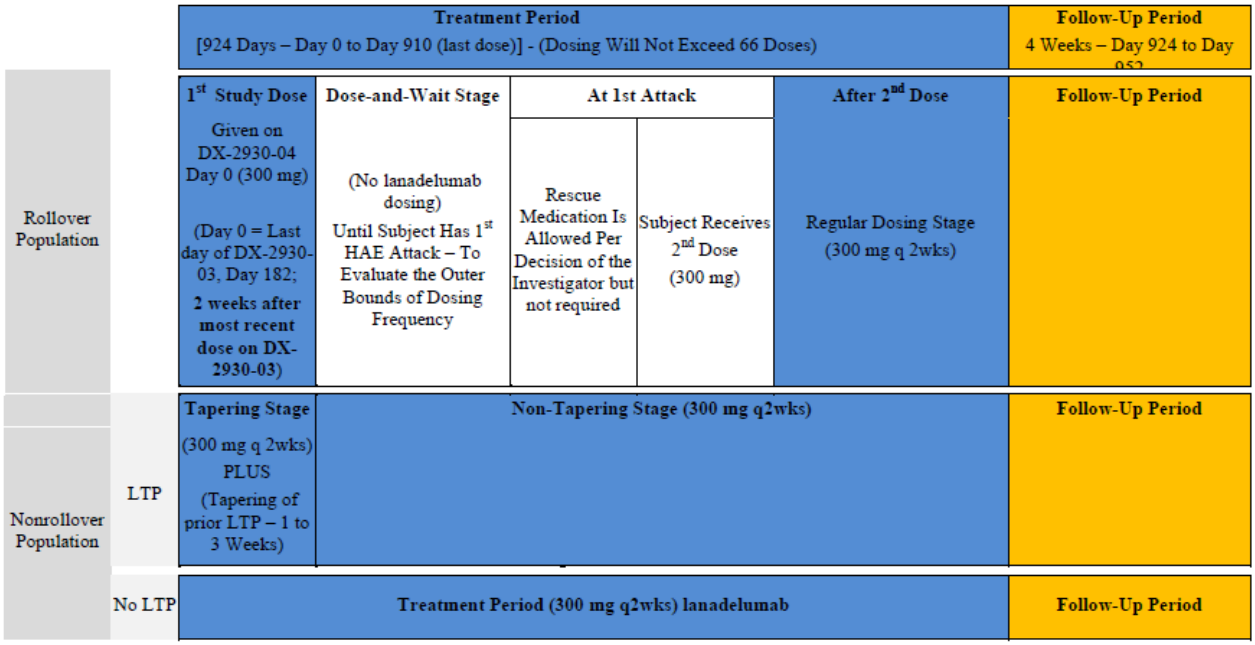


Figure 10 Description of Study Periods



The study is ongoing. An interim analysis covering the first 6 months of the study is included in the MAA (data cut-off date 01 Sep 2017). Therefore, when Study DX-2930-03 and Study DX-2930-04 experiences are combined, the study will provide data covering at least 1 year of exposure for subjects who were previously randomized to the lanadelumab 300 mg q2wks study arm in StudyDX-2930-03.

The selected dosing regimen was based on the results of study DX-2930-03. In order to further evaluate the dosing frequency, rollover subjects from study DX-2930-03 did not have the second dose in study DX-2930-04 until after the first HAE attack ("dose-and-wait").
As opposed to study DX-2930-03, self-administration was allowed after the second dose and after training.

Study Participants

The main inclusion criteria were identical to those of study DX-2930-03, with exception for baseline HAE history. In the pivotal study, at least 1 investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period was required whereas in the extension study, 1 investigator-confirmed HAE attack per 12 weeks was sufficient for eligibility.

Outcome / endpoints

The long-term safety of lanadelumab was the primary endpoint in the study. All efficacy endpoints are secondary.

Key Efficacy Endpoints

- Time from first open-label study dose to the first investigator-confirmed HAE attack for rollover subjects
- Number of investigator-confirmed HAE attacks during the treatment period
- Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period

- Number of moderate or severe investigator-confirmed HAE attacks during the treatment period
- Number of high-morbidity investigator-confirmed HAE attacks during the treatment period

Exploratory efficacy endpoints

- Number and percentage of subjects who are attack-free during the treatment period
- Percentage of HAE attack-free days
- Summary of attack-free period (average duration of an attack-free period)
- Characteristics of investigator-confirmed HAE attacks: Subject level HAE attack characteristics (including attack duration, severity); Event level HAE attack characteristics (HAE attack location, rescue medication use and supportive treatment use for an HAE attack).

Results

Study population

In total, 212 subjects enrolled in the study; 109 from study DX-2930-03 and 103 non-rollovers (whereof 19 subjects from study DX-2930-02).

92.9% of the subjects were active study participants at data lock point for the interim report. 2 subjects had completed the study before extension of the study duration to 30 months. The most common reasons for discontinuing treatment were adverse events and subject withdrawal (each 2.4%).

92% of the subjects had completed 6 months. At the time of the interim analysis, 70 lanadelumab rollover subjects and 5 non-rollover subjects were exposed to lanadelumab for at least 12 months, although the regular dosing period for rollover of subjects on DX-2930-04 was less than 6 months due to the dose-and-wait period. It is noted that one non-rollover subject previously treated with C1-INH discontinued study drug due to lack of efficacy. This subject was negative for neutralising antibodies.

Treated subjects ranged from 12 to 76 years of age, including 21 paediatric subjects (9.9% of subjects) aged 12 to <18 years. Overall median age was 42.8 years.
Enrolled subjects were predominantly female (67.5%). Most subjects were White (93.4%).

The number of historical HAE attacks was lower among the non-rollover than the rollover subjects. This could be explained by the difference in inclusion criteria as described above. Other minor demographic differences between the rollover and non-rollover subjects are not considered relevant for the study results.

Outcomes and estimation

There were no primary efficacy endpoints in the study. All results in study DX-2930-04 are preliminary as the study is still ongoing.

The *time to first investigator-confirmed HAE attack* in rollover subjects is summarised .

Table 18 Estimated Percentage of Subjects with First HAE Attack at Different Weeks

	Assigned Treatment During the DX-2930-03 Study Followed by 1 Dose of 300 mg Lanadelumab on DX-2930-04				
Week	Placebo N=33 (%)	Lanadelumab 150 mg q4w N=26 (%)	Lanadelumab 300 mg q4w N=25 (%)	Lanadelumab 300 mg q2wks N=25 (%)	Total N=109
1 Week	9.1	7.7	4.0	4.0	6.4
2 Weeks	21.2	34.6	24.0	12.0	22.9
3 Weeks	27.3	50.0	32.4	16.0	31.3
4 Weeks	39.4	50.0	49.3	20.0	39.6
6 Weeks	63.6	50.0	49.3	32.0	49.9
8 Weeks	66.7	61.5	58.5	40.0	57.5
10 Weeks	78.8	65.4	67.8	44.0	65.0

At 2 weeks, 78.8% of the former placebo subjects were attack-free, i.e. 21.2% had had their first attack and at 4 weeks post dose, 60.6% were attack-free. The effect of a single dose of lanadelumab waned over time, reaching 36.4% attack-free at 6 weeks. This supports the chosen dosing frequency of every 2-4 weeks.

In analysing the impact of baseline covariates on the time to first attack it was observed that at any given time subjects with BMI classified as overweight or obese have an increased probability of having an attack compared with normal BMI subjects.

The mean number of investigator-confirmed HAE attacks per month (defined as 28 days) was summarized descriptively by study month for each study population.
For non-rollover subjects, the treatment period includes the entire study period; for rollover subjects, the dose-and-wait period is excluded.

Table 19 Mean HAE Attack Rates

Rollover Subjects DX-2930-03 Treatment → DX-2930-04 Study Treatment				Nonrollover Subjects Treatment Prior to the Study→ DX-2930-04 Study Treatment			
Placebo→ 300 q2wks	150 mg q4wks→ 300 q2wks	300 mg q4wks → 300 q2wks	300 mg q2wks→ 300 q2wks	No LTP Use→ 300 q2wks	C1-INH only→ 300 q2wks	Oral Therapy→ 300 q2wks	C1-INH & Oral Therapy→ 300 q2wks
(N=33 subjects)	(N=26 subjects)	(N=25 subjects)	(N=25 subjects)	(N=40 subjects)	(N=53 subjects)	(N=8 subjects)	(N=2 subjects)
Total Subject-Time (Months) for All Subjects							
Baseline period[a]				Baseline period[a]			
29.4	24.5	22.8	23.1	130.3	172.6	26.1	6.5
DX-2930-03 Study Treatment period							
216.1	170.6	163.6	163.5	NA	NA	NA	NA
DX-2930-04 Study Treatment Period				DX-2930-04 Study Treatment period			
239.8	175.9	157.7	147.5	309.8	392.4	56.8	20.5
Mean HAE Attack Rate (attacks/month, SD)							
Baseline (Run in on DX-2930-03)				Baseline (on DX-2930-04)			
3.81 (2.997)	3.18 (1.739)	3.54 (2.580)	3.47 (2.392)	2.56 (2.814)	2.72 (2.919)	1.54 (1.217)	1.69 (0.217)
DX-2930-03 Study Treatment Period							
2.39 (1.935)	0.44 (0.569)	0.54 (0.785)	0.26 (0.451)	NA	NA	NA	NA
DX-2930-04 Study Treatment Period				DX-2930-04 Study Treatment Period[b]			
0.39 (0.897)	0.19 (0.292)	0.47 (0.648)	0.19 (0.303)	0.25 (0.574)	0.32 (0.726)	0.14 (0.240)	0.34 (0.363)
Change in Mean HAE Attack Rate (attacks/month, SD)							
Baseline (Run in on Study DX-2930-03) → end of DX-2930-04[b]							
-3.42 (2.922)	-2.99 (1.753)	-3.10 (2.463)	-3.28 (2.403)	NA	NA	NA	NA
Baseline (Run in on Study DX-2930-03) → end of DX-2930-04[c] Percentage Change							
-90.718	-90.472	-83.862	-94.479	NA	NA	NA	NA
(15.3235)	(21.9941)	(21.6526)	(8.9982)				
End of DX-2930-03→DX-2930-04 interim analysis[d]				Baseline→DX-2930-04 interim analysis			
-2.00 (1.964)	-0.26 (0.326)	-0.12 (0.586)	-0.08 (0.378)	-2.32 (2.461)	-2.40 (2.856)	-1.40 (1.075)	-1.35 (0.146)

a For rollover subjects, the total subject time for the baseline was determined based on a pre-treatment run-in period. For non-rollover subjects, the baseline for the non-rollover safety population is defined as historical rate of HAE attacks in the last 3 months prior to screening divided by the number of days the subject contributed to the historical reporting period multiplied by 28 days.

b Change from Baseline Run In Period to End of Study DX-2930-03 Study Treatment Period,

c Change from End of Treatment period of DX-2930-03 to Treatment Period at Time of Interim Analysis.

d Change from End of Treatment period of DX-2930-03 to Treatment Period at Time of Interim Analysis.

e Change from End of Treatment period of DX-2930-03 to Treatment Period at Time of Interim Analysis.

Rollover subjects began the pivotal study with an overall higher baseline mean attack rate (3.52 attacks per month) than did the non-rollover subjects (2.55 attacks per month), consistent with differences in the eligibility criterion of the study.

For subjects previously treated with lanadelumab in study DX-2930-03, the lanadelumab effect on HAE attack rate was maintained. In non-rollover subjects and in rollover placebo subjects, the mean HAE attack rate decreased similarly to the findings in study DX-2930-03. All subjects receiving lanadelumab 300 mg q2wks had a median attack rate of 0.00.

The number of investigator-confirmed HAE attacks per month was summarized descriptively. In an ad hoc statistical analysis, placebo and lanadelumab 150 mg q4wks rollover subjects showed a significant decrease in attack rate after transitioning to 300 mg q2wks (p=0.001 and p=0.002, respectively).

In a subgroup analysis for subjects <18 years (N=21), the mean HAE attack rate was 0.18 attacks/months compared to 0.30 attacks/month in the entire population (rollovers and non-rollovers); however, the baseline attack rate was lower among adolescents than in the entire population (1.58 vs 3.05 attacks/month).

Preliminary data on investigator-confirmed *HAE-attacks requiring acute treatment*, *moderate or severe HAE attacks* and *high morbidity attacks* are consistent with the overall reduction of attack rates in the study and with the results in DX-2930-03.

Approximately 50% of the subjects were *attack free* during the treatment period up to data lock point for the interim report. The length of the treatment period varied between individuals due to the dose-and-wait period and to inclusion date in the study.

Table 20 Number and Percentage of Subjects that are Attack-Free During the Treatment Period (Regular Dosing Stage for Rollover Subjects)

Parameter	Rollover Subjects N=109 n (%)	Nonrollover Subjects N=103 n (%)	Total N=212 n (%)
Attack-free during the Treatment Period	54 (49.5)	53 (51.5)	107 (50.5)
Attack-free 1 month after Dosing	78 (71.6)	78 (75.7)	156 (73.6)
Attack-free 3 months after Dosing	51 (46.8)[a]	64 (62.1)	115 (54.2)

a Because of the varied length of time to first attack in the dose-and-wait stage, not all 109 rollover subjects contributed 3 months in the regular dosing stage (time from 2nd open-label dose to the interim data cut).

As DX-2930-04 was the first study allowing self-administration at home, a post hoc analysis compared the *mean HAE attack rate change from baseline in subjects with ≥80% of self-administrations to subjects with ≥80% of staff in-clinic administrations*.

Table 21 Efficacy on Self-Administration: Investigator-confirmed HAE Attack Rate Treatment Period Change from Baseline by Predominant Administration Type (Safety Population)

		Investigator-confirmed HAE Attack Rate: Treatment Period Change from Baseline		
Administration	**Statistic**	**Rollover Subjects N=56**	**Nonrollover Subjects N=41**	**Total N=97**
Subjects with ≥80% Self-Administration	n	56	41	97
	Mean (SD)	-3.9 (2.64)	-2.5 (2.27)	-3.3 (2.58)
Subjects with ≥80% Administration by Study Staff in-clinic	n	31	30	61
	Mean (SD)	-2.3 (1.98)	-1.9 (1.99)	-2.1 (1.98)
Subjects with a Mixture of Administration	n	19	32	51
	Mean (SD)	-2.8 (1.90)	-2.4 (3.36)	-2.5 (2.89)

Table 18 Efficacy on Self-Administration: Investigator-confirmed HAE Attack Rate Treatment Period Change from Baseline by Predominant Administration Type (Safety Population)

		Investigator-confirmed HAE Attack Rate: Treatment Period Change from Baseline		
Administration	Statistic	Rollover Subjects N=106	Nonrollover Subjects N= 103	Total N=209
Subjects with ≥80% Self-Administration	n	56	41	97
	Mean (SD)	-3.9 (2.64)	-2.5 (2.27)	-3.3 (2.58)
Subjects with ≥80% Administration by Study Staff in-clinic	n	31	30	61
	Mean (SD)	-2.3 (1.98)	-1.9 (1.99)	-2.1 (1.98)
Subjects with a Mixture of Administration	n	19	32	51
	Mean (SD)	-2.8 (1.90)	-2.4 (3.36)	-2.5 (2.89)

Note: Baseline HAE attack rate for the rollover safety population is defined as the number of investigator-confirmed HAE attacks occurring during the run-in period of DX-2930-03 divided by the total number of days in the run-in period multiplied by 28 days.

Baseline rate for the non-rollover safety population is defined as historical rate of HAE attacks in the last 3 months prior to screening divided by the number of days the subject contributed to the historical reporting period multiplied by 28 days.

Mean decrease in attack rates was -3.3 attacks/month in the self-administration group and -2.1 in the staff assistance group; however, the standard deviations were large and the baseline HAE attack rate was higher in the self-administration group (3.6 vs 2.4 attacks/month). In spite of these uncertainties, it is considered that administration type does not affect lanadelumab efficacy to a relevant extent. This is supported by population PK data, where similar exposure of lanadelumab was seen following SC administration by either health care provider or self-administration.

HAE attacks were collected in study DX-2930-04 following a similar standardized manner similar to that of study DX-2930-03. Attacks were initially reported by patients or their family members, then investigator confirmed. This facilitates comparisons between the two studies. Clinically meaningful improvements were observed in AE-QoL and domain scores (i.e., changes in the AE-QoL total score of at least 6 points) between baseline and 6 months during the study. Mean AE-QoL scores were reduced (i.e., improved for rollover and non-rollover subjects).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme for lanadelumab consists of one pivotal study supported by interim data from a long-term open label extension study and data from a "proof-of concept"/dose-finding study.

DX-2930-03

The pivotal study, DX-2930-03, was a Phase 3, multicentre, randomized, double-blind, placebo-controlled HAE prevention study with a 26-week long treatment duration. One hundred and twenty five subjects (115 adults and 10 adolescents aged 12-≤18) were included in study DX-2930-03 and treated with placebo (N=41) or lanadelumab (N=84). Among the adolescents, 4 were treated with placebo and 6 received lanadelumab. The limited sample size is considered acceptable given the rareness of the condition. Three different lanadelumab dosing regimens were compared to placebo.

The main eligibility criteria were subjects ≥12 years of age with HAE and at least 1 investigator-confirmed HAE attack per 4 weeks. The inclusion of adolescents is strongly endorsed as HAE is a congenital condition which usually becomes more severe from adolescence.

The primary efficacy endpoint in the pivotal study DX-2930-03 was the number of investigator confirmed HAE attacks during the treatment period (Day 0 through Day 182) and the secondary endpoints by rank order were the number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182), the number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182) and the number of investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182. The endpoints of the study are acceptable. It is however noted that the secondary efficacy endpoints are not independent of the primary endpoint, i.e. the same results are in part included in both the primary and secondary endpoints. This is considered a form of redundancy. However, the exploratory endpoints are at least in part independent of the primary endpoint.

Patients were allowed to exit earlier during the run-in period if they experienced 3 or more attacks. The proportion of patients exiting the run-in period (i.e. after randomisation but before treatment) in advance was comparable across randomisation arms (~40% randomised subjects in each arm). Consequently, if the baseline HAE attack rate is overestimated due to these 'escape' patients, this bias applies to all randomisation arms.

DX-2930-02

Study DX-2930-02 was a small dose-ascending study including in total 37 subjects (13 placebo, 24 lanadelumab). The main objective of the study was to assess safety and tolerability.

The baseline demographics in the treatment arms were balanced comparing placebo and total lanadelumab with the exception of gender. There was however some imbalance between the different lanadelumab treatment arms in several parameters. The most prominent difference was seen in the number of HAE attacks which ranged from 7.0 attacks in the last 12 months in the lanadelumab 30 mg arm to 35.2 in the lanadelumab 400 mg arm (placebo 22.7). However the difficulties to get the treatment arms balanced due to low number of subjects in each arm (N=4-11) are acknowledged.

DX-2930-04

Study DX-2930-04 was an open-label long term extension study. All subjects received lanadelumab 300 mg q2wks. In total, 212 subjects enrolled in the study; 109 from study DX-2930-03 ("rollovers") and 103

"non-rollovers" (whereof 19 subjects from study DX-2930-02). In total 21 subjects ≥12 to <18 years are included in the study. The study is still ongoing.

The main objective of the study was safety. There were no primary efficacy endpoints in the study and the efficacy data are mainly descriptive.

Dosing regimen considerations

Election of lanadelumab dose for the pivotal Phase 3 DX-2930-03 study was accomplished by the sponsor using the safety, PK, and PD data generated in the Phase 1 studies DX-2930-01 (healthy subjects) and DX-2930-02 (subjects with HAE). The planned range of lanadelumab dosing for the clinical development program was based upon estimation of the level of plasma kallikrein (pKal) inhibition necessary to attain effective prophylaxis against HAE attacks. It was hypothesized that the necessary molar concentration of lanadelumab would correspond to the average C_{max} attained following administration of ecallantide, a biologic pKal inhibitor. The C_{max} obtained following ecallantide administration is approximately 80 nM or 586 ng/mL.

Drug exposure appeared to be dose-proportional and consistent with the results obtained in healthy subjects in Study DX-2930-01. In study DX-2930-02, two lanadelumab doses of 300 mg or greater administered 2 weeks apart resulted in a normalization of plasma cHMWK levels and a reduction in HAE attacks. Steady-state trough concentrations predicted using PK parameters determined in Study DX-2930-02 indicated that the plasma concentration of lanadelumab after two administrations of 300 mg 2 weeks apart was approximately 27,000 ng/mL (180 nM).

Doses of 300 mg or 150 mg lanadelumab administered every 4 weeks would result in a steady-state trough concentration of approximately 9,500 and 4,750 ng/ml, respectively. These trough levels bracket the Cmax observed in the 100 mg dose group in Study DX-2930-02, which demonstrated a slight, but not statistically significant, reduction in cHMWK levels.

The 3 dose-regimen combinations, 150 mg q4wks, 300 mg q4wks, and 300 mg q2wks, were used in the pivotal study DX-2930-03 provided a 6-fold range of steady-state trough concentrations and leveraged both the biomarker and efficacy data generated in Study DX-2930-02. The dosing regimen 150 mg q2wks has not been studied. It is considered that the dosage of 150 mg should have been evaluated in the phase 2 study and, if relevant, as 150mg q2w in the phase 3 study; 150 mg q2wks could be sufficient for example for an subject weighing 50 kg. Upon CHMP request, the Applicant provided extrapolations of the exposure to lanadelumab for 150 mg q2w. The lanadelumab 150 mg q2wks dosing regimen is not recommended in adult patients since the average $C_{ave,ss}$ (14,200 ng/ml) of lanadelumab is expected to be lower than the IC_{90} for cHMWK (18,777 ng/ml) and the IC_{90} for the monthly rate of HAE attack (33,900 ng/ml).

Efficacy data and additional analyses

Efficacy data

Pivotal study DX-2930-03

The baseline demographics were not fully balanced across the treatment groups.
The proportion of male subjects was 17.1% in the placebo arm vs 35.7% in the lanadelumab arms, ranging from 28.6% in the 150 mg q4wks arm to 44.4% in the 300 mg q2wks arm. This is notable, since there are publications indicating a more severe disease in women. Randomization was stratified by the baseline attack rate observed during the run-in period. The imbalance in gender between the treatment arms therefore indicates that there was no major correlation between gender and attack frequency. This is also supported by

subgroup analysis, where no treatment differences regarding gender compared to the entire population were detected.
Furthermore, the proportion of black/African American subjects was higher in the lanadelumab 300 mg q4wks arm than in the other treatment arms including placebo (20.7% vs 3.6-4.9%). However, in total, only 12 subjects with other race than white were included in the study. Subgroup analyses are hampered by the low number of subjects.
Of note, European centres represented only 5 / 41 centres with 29/126 randomized patients.

The primary endpoint of the pivotal study was the number of investigator conformed HAE attacks during the 6 month treatment period, expressed as HAE attack rate (mean HAE attacks/4 weeks).

The number of investigator confirmed HAE attacks during the treatment period was reduced in all lanadelumab treatment arms compared to placebo ($p<0.001$ for all lanadelumab arms vs placebo). The relative risk reduction compared to placebo ranged from 73% in the 300 mg q4wks arm to 87% in the 300 mg q2wks arm, corresponding to a decrease of approximately 1.5 attack/4 weeks in the 150 mg q4wks and 300 mg q4wks arms and 1.75 attacks/4 weeks in the 300 mg q2wks treatment arm based on LS mean HAE attack rate in the four treatment arms.

Based on both the primary analysis (model-based) and crude rates, it seems there was a “placebo effect” in the DX-2930-03 trial, as 1/3 of patients in the placebo achieved ≥50 % reduction of HAE attacks. The causes of this cannot be fully determined and will remain unclear. Nevertheless, the presence of a study effect across all arms does not impact the conclusions on the comparison of the attack rate between the arms during the treatment period, which was the primary objective.

In spite of stratification by the baseline attack rate observed during the run-in period, the mean rate of HAE attacks during run-in was not fully balanced and the standard deviations [SD] were large (placebo: 4.02 [3.26] attacks/4 weeks; lanadelumab 150 mg q4wks 3.22 [1.83], lanadelumab 300 mg q4wks 3.71 [2.51] and lanadelumab 300 mg q2wks 3.52 [2.33]). This could be due to the highest stratum being indefinitely large (≥3 attacks/4 weeks). Nevertheless, this may have impact on the robustness of the data.
The primary efficacy analysis was a Poisson model with HAE attack rate during the baseline (run-in) period included as a covariate. The Applicant has provided an overview on the effect of baseline attack rate on attack rate during the trial, including a subgroup analysis on HAE attack rate based on run-in period HAE attack rate. Data provided confirm that the treatment period attack rate was strongly influenced by the baseline attack rate (the higher the run-in period attack rate, the higher the treatment period attack rate). In all subgroups, the decrease in HAE attack rate was larger in the lanadelumab treatment arms compared to placebo. These changes were statistically significant at the 0.05 level, with the exception of 150 mg every 4 weeks in the subgroup Run-in HAE attack rate 1-<2 attacks/month. Furthermore, the Applicant has provided data on the absolute change from baseline in each treatment arm for the primary and secondary endpoints. For all endpoints, the change from baseline was 38-40% in the placebo arm and 84-86%, 84-97% and 88-92% for lanadelumab 150 mg q4w, 300 mg q4w and 300 mg q2w, respectively. This is considered to be of clinical relevance.

For the primary endpoint, pre-specified subgroup analyses were performed. Results from subgroup analyses were generally consistent with the results from the entire population

In the pivotal study, there were three secondary efficacy endpoints. Lanadelumab treatment reduced the number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182), the number of moderate or severe investigator-confirmed HAE attacks during the treatment period and the number of investigator-confirmed HAE attacks occurring on Day 14 through Day 182 compared to placebo. The exploratory analyses included proportion of subjects with severe attacks, median time to the

first investigator confirmed HAE attack, responder rate analyses and total and all domain (functioning, fatigue/mood, fear/shame, and nutrition) quality of life scores. The exploratory analyses support the results from the primary endpoint of a beneficial effect of lanadelumab compared to placebo.

Study DX-2930-02

The primary efficacy endpoint was the number of HAE attacks per week from Day 8 to Day 50. The mean number of HAE attacks/week was lower in subjects treated with two doses of lanadelumab 300 mg or 400 mg (mean [SD] 0.034 [0.129]) compared to placebo (0.364 [0.364]) (p=0.0012). The effects on HAE attacks were strongly associated with drug exposure, corroborating the results of the primary efficacy analysis.

The beneficial effect of lanadelumab in prevention of HAE-attacks was further supported by a post hoc analysis comparing mean lanadelumab concentration with incidence of HAE attacks indicating a correlation between lanadelumab exposure and the number of attacks.

Extension study DX-2930-04

All results in study DX-2930-04 are preliminary as the study is still ongoing.

The number of investigator-confirmed HAE attacks per month was summarized descriptively. For subjects previously treated with lanadelumab in study DX-2930-03, the effect from the pivotal study was maintained.

In non-rollover subjects, the mean HAE attack rate decreased from 1.54-2.72 attacks/month at baseline to 0.14-0.34 attacks/month at interim analysis and in rollover placebo subjects from 3.81 to 0.39 attacks/month. This is in concordance with the findings in study DX-2930-03.
At the time of the interim analysis (including 12 months of lanadelumab exposure across both studies for 75 subjects), all subjects receiving lanadelumab 300 mg q2wks had a median attack rate of 0.00. This indicates a sustained effect of lanadelumab.
In an ad hoc statistical analysis, placebo and lanadelumab 150 mg q4wks rollover subjects showed a significant decrease in attack rate after transitioning to 300 mg q2wks (p=0.001 and p=0.002, respectively).

The preliminary data on investigator-confirmed HAE-attacks requiring acute treatment, moderate or severe HAE attacks and high morbidity attacks are consistent with the overall reduction of attack rates in the study and with the results in DX-2930-03.

Subjects <18 years

8.0% of the subjects in the pivotal study were adolescents aged ≥12 to <18 years; however, the absolute number of adolescents subjects was low (N = 10; placebo 4, lanadelumab 6). In the extension study DX-2930-04, 21 subjects ≥12 to <18 years (9.9% of study population) were treated with lanadelumab, including 8 rollovers from DX-2930-03. Overall, 23 unique paediatric subjects received lanadelumab in one or both studies: 2 paediatric subjects in Study DX-2930-03 only and 17 paediatric subjects in Study DX-2930-04 only (4 placebo-treated rollover subjects and 13 non-rollover subjects); 4 subjects were counted as paediatric subjects in both studies.
Of the 23 paediatric subjects across the 2 Phase 3 studies, 14 subjects were in 12-14 years age group, while 9 subjects were in 15-17 years age group.

The highest weight based dose evaluated is 3.0 mg /kg which correspond to 120 mg for an adolescent (weighing about 40 kg) and to 150 to 240 mg for an adult weighing (50 to 80 kg).In the population pharmacokinetic modelling, an approximately 37% higher exposure in adolescents than adults (18 to 65 years) was predicted, as expected due to an overall lower body weight in adolescents. However, the AUC range was quite large; 121- 832 ug*d/ml in adults and 321-1050 ug*d/mL in adolescents. It was considered less probable that the additional

exposure in adolescents will exert any major impact on efficacy and safety. The difference in exposure between adults and adolescents are considered to be secondary to differences in mean weight between the two groups.

As in the entire population, the HAE attack rate was numerically lower in lanadelumab treated subjects than in placebo treated subjects in study DX-2930-03; however, the number of subjects in this subgroup was low and the 95% confidence intervals covered 1. However, a lower effect in adolescents is not anticipated, given the slightly higher exposure. In study DX-2930-04, the mean HAE attack rate was 0.18 attacks/months in subjects <18 years compared to 0.30 attacks/month in the entire population (rollovers and non-rollovers); however, the baseline attack rate was lower among adolescents than in the entire population (1.58 vs 3.05 attacks/month). In summary, data in adolescents is limited. Nevertheless, HAE usually presents during childhood or adolescence with intermittent episodes of potentially life-threatening angioedema. Indication

The Applicant has proposed the following wording of the indication *"[Lanadelumab] is indicated for routine prevention of attacks of hereditary angioedema (HAE) in patients aged 12 years and older".*

The wording "routine" indicates that the prevention is given on an everyday basis as opposed to prevention given e.g. before surgery. This is endorsed by CHMP.

The eligibility criteria in the pivotal study included a baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks, i.e. a subset of HAE subjects with frequent attacks. Upon request, the Applicant has provided a summary of the baseline HAE attack characteristics in studies DX-2930-02, DX-2930-03 and DX-2930-04 as well as an overview of efficacy and safety in study DX-2930-04 in different baseline HAE attack rate subgroups. Data provided confirm that the treatment period attack rate was strongly influenced by the baseline attack rate (the higher the run-in period attack rate, the higher the treatment period attack rate). However, effect was shown in all investigated HAE attack rate groups. The posology reflects that lanadelumab should be used only in subjects with recurrent HAE attacks. Additionally, the SmPC clearly mentions that lanadelumab cannot be used for treatment of acute attacks.

In all clinical studies, only subjects with HAE type I or II were included. Those conditions are characterised by either a deficiency or a dysfunction of C1-esterase inhibitor (C1-INH), leading to dysregulation of plasma kallikrein activity. "HAE with normal C1-INH activity", i.e. HAE other than HAE1 or HAE2 is a heterogeneous entity comprising of e.g. HAE caused by mutations in the coagulation factor XII (F12) gene, the plasminogen (PLG) gene, or the angiopoietin-1 gene (ANGPT1). In many cases the aetiology is unknown.

The applicant was asked to discuss whether the results on HAE type I and II could be extrapolated to other forms of HAE. The applicant presented supporting information from literature that subjects with F12-HAE and PLG-HAE may have an increased FXII activation, implicating a role for the kallikrein-kinin system in angioedema formation also in this population. The CHMP agreed that extrapolation to other forms of HAE is acceptable since the kallikrein-kinin system may be involved also in other forms of "HAE with normal C1-INH activity". Therefore, given the severity of the disease and based on this theoretical rationale for extrapolating the effect to subjects with other forms of HAE, the general wording "HAE" rather than "HAE type I and II" is accepted. Additionally, the absence of data for subjects with HAE with normal C1 INH-activity- is adequately stated in sections 4.4 and 5.1 of the SmPC.

Posology

The proposed starting dose 300 mg q2w is supported by PK and PD data. As study DX-2930-03 was not powered to detect differences in efficacy between the different lanadelumab treatment arms, no statistical comparisons of the treatment difference in the three lanadelumab treatment arms were made. In the pivotal study, all

lanadelumab dosing regimens were superior to placebo; however, the effects of lanadelumab were numerically somewhat larger using the dosing regimen 300 mg q2wks. It could be argued that the difference in reduction in mean attack rate relative placebo (87% for 300 mg q2w vs 76% for 150 mg q4w and 73% for 300 mg q4w) is of limited clinical relevance. On the other hand, the LS mean monthly attack rate during treatment in the 300 mg q2w arm was approximately half that of 150 mg q4w and 300 mg q4w (0.26 vs 0.48 and 0.53, respectively), which is considered relevant given that HAE attacks are potentially fatal. Furthermore, the safety data of lanadelumab seems generally benign and the number of AEs in the different treatment arms was comparable. The starting dose 300 mg q2w is therefore acknowledged.

In all studies, overweight subjects were in majority, e.g. 21 subjects with weight ≥100 kg were included in study DX-2930-03. Moreover, in analysing the impact of baseline covariates on the time to first attack it was observed that at any given time subjects with BMI classified as overweight or obese have an increased probability of having an attack compared with normal BMI subjects.

Pharmacokinetic analyses suggest a lower exposure in subjects with higher body weight. An ad hoc subgroup analysis based on weight was performed in study DX-2930-03. Effect on HAE attack rate of 300 mg q2w was shown in all weight subgroups, including subjects ≥100 kg. On the contrary, the dose regimen 150 mg q4w did not exert any effect on HAE attack rate in subjects ≥100 kg. It should be noted that due to the relatively small study, the number of subjects in each subgroup is low. However, the number of subjects in the >100 kg subgroup (N=9) was comparable to the other weight subgroups.
In studyDX-2930-04, the mean percent change from baseline in HAE attack rate in non-rollover subjects ≥100 kg (N=21), was -87.0% [SD15.0], which was comparable with the other weight groups (93.5% [11.6], 68.9% [150.6] and 89.2% [19.0] for weight <50 kg, 50-<75 kg, and 75-<100kg, respectively).
Using PK/PD data, the applicant has clarified that the 300 mg q2wks dosing was associated with lanadelumab exposure approximate or above the IC_{90} of PD and $EAUC_{90}$ for efficacy in patients across a large range of body weight (46.8-150 kg). Taken together, a special dosing regimen for heavy subjects is not considered needed.

Low weight is associated with a higher lanadelumab exposure. Therefore, a lower dose regimen (300 mg Q4w) may considered and is mentioned in the posology section.
No relevant differences between the TEAE profiles for subjects <50 kg compared to other weight groups were identified. The most frequently reported treatment-related TEAE was injection site pain. However, in total, only 7 subjects with weight <50 kg have been included in the two phase 3 studies DX-2930-03 and DX-2930-04.

The highest percentage of subjects (44%) on lanadelumab 300 mg q2wks were attack-free for the entire 26 weeks (~ 6 months) treatment period, and ~ 77% of subjects were attack-free day 70-182 compared to 44% in the 300 mg q4wks dose regimen. The applicant proposes that the dose may be reduced to 300 mg q4wks in subjects who are stably attack free. This is endorsed, especially in subjects with low weight. This is also reflected in the posology.

A post hoc analysis to the ongoing extension study DX-2930-04 compared the mean HAE attack rate change from baseline in subjects with ≥80% of self-administrations to subjects with ≥80% of staff in-clinic administrations. Mean decrease in attack rates was -3.3 attacks/month in the self-administration group and -2.1 in the staff assistance group; however, the standard deviations were large and the baseline HAE attack rate was higher in the self-administration group (3.6 vs 2.4 attacks/month). In spite of these uncertainties, it is considered that administration type does not affect lanadelumab efficacy to a relevant extent. This is supported by population PK data, where similar exposure of lanadelumab was seen following SC administration by either health care provider or self-administration. From an efficacy point of view, self-administration is considered acceptable.

2.5.4. Conclusions on clinical efficacy

The applicant has justified the proposed wording for the therapeutic indication *"[Lanadelumab] is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older"*.

Pivotal study DX-2930-03 met its primary endpoint (the number of investigator conformed HAE attacks during the 6 month treatment period, expressed as HAE attack rate) and the three secondary efficacy endpoints. Numerically, the 300 mg q2wks dose was consistently most effective, although all dosing regimens were more effective than placebo.
The efficacy data are supported by exploratory endpoints and by data from study DX-2930-02 and DX-2930-04.

Although data on mortality are not expected as the clinical data submitted remain limited in term of duration, significant decreases in the number of attacks as well as data on amelioration of the severity of the attacks would possibly lead to a decrease in mortality and improvements in quality of life.

Additionally, the administration via subcutaneous route and frequency of lanadelumab offers an improvement for patient care compared to other substances registered for prevention of HAE attacks in the EU.

2.6. Clinical safety

The safety of lanadelumab was evaluated in four clinical studies:

- DX-2930-01, phase 1, first in human, dose 0.1 to 3.0 mg/kg, randomized, double-blind, placebo-controlled study in healthy adults
- DX-2930-02, phase 1b, dose 30–400 mg, randomized, double-blind, placebo-controlled study in adults with HAE
- DX-2930-03, phase 3, pivotal, randomized, double-blind, placebo-controlled study in subjects aged 12 years or older with HAE
- DX-2930-04, phase 3, open-label study in subjects aged 12 years or older with HAE. Ongoing study, cut-off date of 01 Sep 2017 (updated in response to questions to provide 4 months of additional data, cut-off date 01 Jan 2018)

Study DX-2930-03 allows for direct evaluation of the safety of lanadelumab compared to placebo and is considered the main study for safety assessment, whereas analyses using the pooled lanadelumab-treated population in the phase 3 studies (n=220, out of which 212 subjects had experience from both phase 3 studies and 8 who discontinued/not-rolled over from DX-2930-03) will explore if any new safety signals emerge with longer term exposure and within patient subgroups.

Approximately half (42%) of the 4216 lanadelumab administrations in the Phase 3 studies were self-administered.

In the Phase 3 studies (DX-2390-03 and DX-2930-04), angioedema attacks were reported as AEs and the most frequently reported TEAEs in the Phase 3 studies were HAE attacks. Efficacy endpoints in both studies were related to angioedema attacks.

For the presentation of the safety profile, data from the two Phase 1 studies have not been integrated with the Phase 3 studies because the safety profile of lanadelumab administered to asymptomatic HAE patients and healthy volunteer subjects was considered to possibly be different from the safety profile of HAE patients.

Patient exposure

Table 22

Study Phase - Subject Population Study ID	Treated Subjects		
	Placebo	Lanadelumab	Total
Phase 1 Studies			
DX-2930-01: Single-dose – Healthy	8	24	32
DX-2930-02: Multiple-dose – HAE[a]	13	24	37
Phase 3 Efficacy and Safety Studies - HAE			
DX-2930-03: Placebo-controlled	41	84	125
DX-2930-04: Uncontrolled (OLE)[b]	0	212	212
Unique Subject Exposures	**62**	**257**[c]	**278**[d]

HAE=hereditary angioedema; OLE=open-label extension

[a] Eight placebo-treated and 11 lanadelumab-treated subjects in Study DX-2930-02 subsequently enrolled in Study DX-2930-04. No subject from prior lanadelumab study was allowed in Study DX-2930-03; therefore, no subject from Study DX-2930-02 enrolled into Study DX-2930-03.

[b] 33 placebo-treated and 76 lanadelumab-treated subjects in Study DX-2930-03 rolled over to Study DX-2930-04.

[c] Includes 24 subjects from DX-2930-01, 24 subjects from DX-2930-02, 84 subjects from Study DX-2930-03, and 125 subjects from Study DX-2930-04 (92 non-rollovers not previously exposed to lanadelumab and 33 placebo-treated subjects in Study DX-2930-03 who rolled over).

[d] Includes 8 subjects from DX-2930-01, 5 subjects from DX-2930-02, and 8 subjects from Study DX-2930-03 (did not rollover into Study DX-2930-04) who received placebo only and never received lanadelumab in any clinical study.

Rollovers and non-rollovers in open-label study DX-2930-04

Rollovers: Subjects in DX-2930-04 who had completed the double-blind treatment period at Day 182 of Study DX-2930-03 and consented to enter Study DX-2930-04. The first DX-2930-04 visit for rollover subjects (Day 0) occurred on the same day as the DX-2930-03 Day 182 study visit. Note that rollover subjects could have been in both the active- and placebo group in study DX-2930-03.

Non-rollovers: Subjects who were not participants in Study DX-2930-03; included those who were new to the lanadelumab clinical development program and those who had participated in Study DX-2930-02 i.e. non-rollovers could have been pre-exposed to lanadelumab.

The median total dose received for the lanadelumab-treated population was 4800 mg (range: 300-11,400 mg). The highest exposure was for subjects who received 300 mg q2wk across both phase 3 studies (8100 mg median total dose) and lowest exposure was for placebo-rollover subjects and non-rollovers subjects participating in Study DX-2930-04 (4500 mg median total dose).

205/220 (93%) received exposure to lanadelumab for at least 6 months and 50% (110/220) of subjects were exposed for ≥9 months. 75 subjects had at least 1 year of cumulative study experience with lanadelumab. 70/75 were rollovers with experience on Study DX-2930-03 and Study DX-2930-04.

The demographic profile of subjects included in the phase 3 trials in US, Canada, Jordan and Europe is generally considered representative for HAE patients, although it is noted that overweight and obese patients might be overrepresented. It is also noted that the ethnicity of the safety population is almost exclusively white.

Lanadelumab is intended for long-term treatment of HAE. However, only 75 subjects have been exposed for one year in the study program.

Adverse events

Phase 3 Studies

Table 23 Study DX-2930-03 Overall summary of TEAEs (excluding HAE attack adverse events) during the treatment period (day 0 to day 182)

	Placebo	Lanadelumab			
Category	N=41 n (%) m	150 mg q4wks N=28 n (%) m	300 mg q4wks N=29 n (%) m	300 mg q2wks N=27 n (%) m	Overall N=84 n (%) m
Any TEAE	31 (75.6) 231	25 (89.3) 268	25 (86.2) 182	26 (96.3) 235	76 (90.5) 685
Any Related TEAE	14 (34.1) 85	17 (60.7) 167	14 (48.3) 121	19 (70.4) 131	50 (59.5) 419
Any Serious TEAE	0	0	3 (10.3) 3	1 (3.7) 1	4 (4.8) 4
Risk Difference		0	10.34	3.70	4.76
(95% CI of Risk Difference)		NE	(-13.36, 33.42)	(-20.34, 27.39)	(-14.20, 23.47)
Any Related Serious TEAE	0	0	0	0	0
Any Severe TEAE	4 (9.8) 7	2 (7.1) 2	4 (13.8) 6	2 (7.4) 2	8 (9.5) 10
Any Related Severe TEAE	1 (2.4) 4	0	1 (3.4) 2	0	1 (1.2) 2
Any Investigator-reported AESI	0	1 (3.6) 2	1 (3.4) 2	3 (11.1) 4	5 (6.0) 8
Risk Difference		3.57	3.45	11.11	5.95
(95% CI of Risk Difference)		(-20.32, 26.96	(-20.22, 26.91)	(-13.17, 34.31)	(-13.03, 24.62)
Deaths due to TEAE	0	0	0	0	0
Hospitalizations due to TEAE[a]	0	0	3 (10.3) 3	1 (3.7) 1	4 (4.8) 4
Discontinuation due to TEAE	1 (2.4) -	0	1 (3.4) -	0	1 (1.2) -

Abbreviations: AESI=adverse event of special interest; HAE=hereditary angioedema; n=number of subjects experiencing the event, m=number of events; NE=nonestimated.
Percentages are based on all subjects in the safety population. Subjects were counted once per category per treatment.
TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.
Related TEAEs are TEAEs classified as related to study drug by the investigator.
Severe TEAEs are TEAEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.
Non-HAE attack reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.
95% CI for relative risk is calculated by exact method.
If 0 events occurred in a treatment group, a value of 0.5 was added in order to calculate relative risks.
[a] Hospitalizations were due to SAEs.

Overall, there were more TEAEs in the lanadelumab treated group compared to placebo, 91% vs 76%, more related TEAEs 60% vs 34% and more serious TEAEs 5% vs 0%. Numerically there is a trend that the highest dose group, 300 mg q2 wks, had more TEAEs and more related TEAEs compared to the other lanadelumab groups.

However, no deaths and no related serious TEAEs were reported during the study.

Table 24 Study DX-2930-04 Overall summary of TEAEs (excluding HAE attack adverse events) during the treatment period

Category	Lanadelumab 300 q2wks		
	Rollover Subjects N=109 n (%) m	Nonrollover Subjects N=103 n (%) m	Total N=212 n (%) m
Total Subject-time (years)[a]	73.75	59.75	133.50
Mean Subject-time (years)	0.68	0.58	0.63
Total Number of Doses[b]	1590	1567	3157
Mean Number of Doses	14.6	15.2	14.9
Any TEAE	95 (87.2) 760	87 (84.5) 771	182 (85.8) 1531
Any Related TEAE	36 (33.0) 287	53 (51.5) 427	89 (42.0) 714
Any Serious TEAE	5 (4.6) 6	3 (2.9) 5	8 (3.8) 11
Any Related Serious TEAE	0	0	0
Any Severe TEAE	10 (9.2) 12	11 (10.7) 16	21 (9.9) 28
Any Related Severe TEAE	0	3 (2.9) 5	3 (1.4) 5
Any Investigator-reported AESI	4 (3.7) 8	4 (3.9) 5	8 (3.8) 13
Deaths due to TEAE	0	0	0
Hospitalizations due to TEAE[c]	5 (4.6) 6	3 (2.9) 5	8 (3.8) 11
Discontinuation due to TEAE	1 (0.9) -	4 (3.9) -	5 (2.4) -

Abbreviations: AESI=adverse event of special interest; HAE=hereditary angioedema; n=number of subjects experiencing the event, m=number of events; TEAE=treatment-emergent adverse event.
Percentages are based on all subjects in the safety population. Subjects were counted once per category per treatment.
TEAEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.
Related TEAEs are TEAEs classified as related to study drug by the investigator.
Severe TEAEs are TEAEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.
Non-HAE attack reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.
AESIs are AEs of special interest as determined by the investigator.
[a] A year is defined as 365.25 days. Total subject-time (years) is the combined duration of subject exposures in years.
[b] Sum of all doses for all subjects.
[c] Hospitalizations were due to SAEs.

In study DX-2930-04 all subjects were exposed to the same lanadelumab dose. Exposure time for roll-over subjects are generally longer than for non-rollovers. Nevertheless, no major difference between roll-overs and non-rollovers was observed. No deaths and no related serious TEAEs were reported during the study. There were few discontinuations.

Treatment-emergent HAE attacks reported as AEs

Study DX-2930-03

Fifty two of 84 subjects (62%) in the 3 lanadelumab treatment arms had at least 1 treatment-emergent HAE attack reported events: 17/28 (61%) in the 150 mg q4wks arm, 20/29 (69%) subjects in the 300 mg q4wks arm, 15/27 (56%) subjects in the 300 mg q2 wks arm, and 40/41 subjects (98%) in the placebo arm. There were 239 TEAEs in the 3 lanadelumab treatment arms and 577 TEAEs in the placebo arm.

No subject in the lanadelumab treatment arms had a related treatment-emergent HAE attack AE. Two of 41 subjects (4.9%) in the placebo arm had 19 related treatment-emergent HAE attacks.

One SAE occurred in 1/84 lanadelumab-treated subjects (1.2%) and 1/41 placebo-treated subjects (2.4%) had an SAE. None of the SAEs were considered related to the study treatment.

12/84 (14%) subjects in the lanadelumab treatment arms had a severe TEAE: 5/28 (18%) subjects in the 150mg q4wks arm, 5/29 (17%) subjects in the 300 mg q4wks arm,

2/27 subjects (7.4%) in the lanadelumab 300 mg q2wks arm, and 11/41 (27%) in the placebo arm. One severe TEAE was considered related to the study treatment.

One subject in the placebo arm discontinued due to a treatment emergent HAE attack.

It is acknowledged that in the placebo controlled study DX-2930-03, fewer lanadelumab treated subjects experienced HAE attacks (62% vs 98%) reported as adverse events and that also severe HAE attacks numerically were reduced compared to placebo.

Study DX-2930-04

75% of subjects experienced HAE attacks reported as TEAEs. The protocol required rollover subjects to have 1 attack before regular dosing commenced. Therefore, virtually all of the rollover subjects had at least 1 HAE attack (98%) when the "dose-and-wait" stage prior to regular dosing was included in the analysis. When excluding the results from the "dose-and-wait" stage, 49% rollover subjects experienced HAE attacks reported as TEAEs (ie, during the regular dosing stage). All non-rollover subjects began to receive regular dosing starting on Day 0 of the study; 51% experienced HAE attacks during the treatment period.

Common adverse events

Study DX-2930-03

Table 25 Common adverse events, TEAEs that occurred in ⩾5% of subjects in overall safety population in Study DX-2930-03

		Lanadelumab			
Preferred Term	**Placebo N=41 n (%) m**	**150 mg q4wks (N=28) n (%) m**	**300 mg q4wks (N=29) n (%) m**	**300 mg q2wks (N=27) n (%) m**	**Total (N=84) n (%) m**
Any TEAE	31 (75.6) 231	25 (89.3) 268	25 (86.2) 182	26 (96.3) 235	76 (90.5) 685
Injection site pain	12 (29.3) 74	13 (46.4) 129	9 (31.0) 74	14 (51.9) 72	36 (42.9) 275
Viral upper respiratory tract infection	11 (26.8) 16	3 (10.7) 5	7 (24.1) 10	10 (37.0) 12	20 (23.8) 27
Headache	8 (19.5) 10	3 (10.7) 10	5 (17.2) 8	9 (33.3) 18	17 (20.2) 36
Injection site erythema	1 (2.4) 1	4 (14.3) 23	2 (6.9) 6	2 (7.4) 7	8 (9.5) 36
Injection site bruising	0	3 (10.7) 5	2 (6.9) 2	1 (3.7) 1	6 (7.1) 8
Dizziness	0	1 (3.6) 2	3 (10.3) 5	1 (3.7) 1	5 (6.0) 8

In study DX-2930-03, injection site reactions are the most common TEAE, which are further discussed in the AESI section. Among the most common adverse events reported in study DX-2930-03 were viral respiratory upper tract infections; these adverse events were equally common in both groups. Headache was also commonly reported, with the same rate in actively and placebo-treated patients.

Table 26 Study DX-2930-03 Related TEAEs (excluding HAE attack reported events) during the treatment period (day 0 to day 182)

System Organ Class Preferred Term	Placebo N=41 n (%) m	Lanadelumab 150 mg q4wks (N=28) n (%) m	Lanadelumab 300 mg q4wks (N=29) n (%) m	Lanadelumab 300 mg q2wks (N=27) n (%) m	Lanadelumab Total (N=84) n (%) m
Any Related TEAE	14 (34.1) 85	17 (60.7) 167	14 (48.3) 121	19 (70.4) 131	50 (59.5) 419
Gastrointestinal disorders	0	0	0	1 (3.7) 1	1 (1.2) 1
Paraesthesia oral	0	0	0	1 (3.7) 1	1 (1.2) 1
General disorders and administration site conditions	12 (29.3) 77	15 (53.6) 162	13 (44.8) 113	15 (55.6) 117	43 (51.2) 392
Injection site pain	11 (26.8) 69	12 (42.9) 125	9 (31.0) 74	14 (51.9) 71	35 (41.7) 270
Injection site erythema	1 (2.4) 1	4 (14.3) 23	2 (6.9) 6	2 (7.4) 7	8 (9.5) 36
Injection site bruising	0	2 (7.1) 4	2 (6.9) 2	1 (3.7) 1	5 (6.0) 7
Injection site discomfort	0	0	2 (6.9) 13	1 (3.7) 10	3 (3.6) 23
Injection site haemorrhage	1 (2.4) 7	1 (3.6) 2	0	2 (7.4) 11	3 (3.6) 13
Injection site pruritus	0	1 (3.6) 1	2 (6.9) 2	0	3 (3.6) 3
Injection site swelling	0	1 (3.6) 1	1 (3.4) 9	1 (3.7) 3	3 (3.6) 13
Injection site haematoma	0	0	1 (3.4) 2	1 (3.7) 1	2 (2.4) 3
Injection site induration	0	1 (3.6) 2	1 (3.4) 1	0	2 (2.4) 3
Injection site paraesthesia	0	2 (7.1) 2	0	0	2 (2.4) 2
Injection site reaction	0	0	1 (3.4) 1	1 (3.7) 1	2 (2.4) 2
Injection site warmth	0	0	1 (3.4) 3	1 (3.7) 11	2 (2.4) 14
Injection site oedema	0	0	0	1 (3.7) 1	1 (1.2) 1
Injection site rash	0	1 (3.6) 1	0	0	1 (1.2) 1
Malaise	0	1 (3.6) 1	0	0	1 (1.2) 1
Immune system disorders	0	0	0	1 (3.7) 2	1 (1.2) 2
Hypersensitivity	0	0	0	1 (3.7) 2	1 (1.2) 2
Investigations	1 (2.4) 1	0	1 (3.4) 2	0	1 (1.2) 2
Alanine aminotransferase increased	0	0	1 (3.4) 1	0	1 (1.2) 1
Aspartate aminotransferase increased	0	0	1 (3.4) 1	0	1 (1.2) 1
Prothrombin time prolonged	1 (2.4) 1	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (3.7) 1	1 (1.2) 1
Myalgia	0	0	0	1 (3.7) 1	1 (1.2) 1
Nervous system disorders	3 (7.3) 7	3 (10.7) 4	3 (10.3) 6	4 (14.8) 10	10 (11.9) 20
Headache	1 (2.4) 3	1 (3.6) 2	2 (6.9) 4	3 (11.1) 7	6 (7.1) 13
Dysgeusia	1 (2.4) 3	1 (3.6) 1	0	1 (3.7) 1	2 (2.4) 2
Dizziness	0	0	1 (3.4) 2	0	1 (1.2) 2
Paraesthesia	0	1 (3.6) 1	0	0	1 (1.2) 1
Somnolence	0	0	0	1 (3.7) 2	1 (1.2) 2
Tension headache	1 (2.4) 1	0	0	0	0
Skin and subcutaneous tissue disorders	0	1 (3.6) 1	0	0	1 (1.2) 1
Rash maculo-papular	0	1 (3.6) 1	0	0	1 (1.2) 1

In study DX-2930-03, related TEAEs are dominated by injection site reactions, which are further discussed in the AESI section.

Injection site reactions are also common in the ongoing open-label study (DX-2930-04).

Serious adverse event / deaths / other significant events

No deaths occurred during any of the clinical studies.

Phase 3 studies:

Study DX-2930-03
Serious TEAEs were reported by 4 lanadelumab-treated subjects (catheter site infection, pyelonephritis, meniscus injury, and bipolar II disorder). None of the SAEs was considered related to the study treatment. All four subjects were hospitalized due to the serious TEAEs.

No placebo-treated subject reported an SAE.

Study DX-2930-04
8 subjects experienced 11 SAEs. None of the SAEs were considered related and were different diagnoses with no observable pattern.

One subject reporting SAE events of upper GI haemorrhage and suspected pneumonia after accidental ingestion of a caustic solution [hypochlorite]) discontinued the study as a result.

One subject reported an SAE in both Study DX-2930-03 (bipolar II disorder) and Study DX-2930-04 (lumbar spinal stenosis).

One subject was diagnosed with relapsed gluteal fibrosarcoma and continued the study after the surgery. This was the only malignancy reported during the conduct of the lanadelumab clinical studies.

Table 27 Serious TEAEs (Excluding HAE Attack Adverse Events) in the Lanadelumab-treated Population in DX-2930-03 and DX-2930-04

System Organ Class Preferred Term	150 mg q4wks ↓ 300 mg q2wks N=28 n (%) m	300 mg q4wks ↓ 300 mg q2wks N=29 n (%) m	300 mg q2wks ↓ 300 mg q2wks N=27 n (%) m	Placebo ROs and Nonrollovers N=136 n (%) m	Lanadelumab-treated Population N=220 n (%) m
Any Serious TEAE	1 (3.6) 2	3 (10.3) 4	2 (7.4) 2	5 (3.7) 7	11 (5.0) 15
Gastrointestinal disorders	**1 (3.6) 1**	**0**	**0**	**1 (0.7) 1**	**2 (0.9) 2**
Anal fissure	0	0	0	1 (0.7) 1	1 (0.5) 1
Upper gastrointestinal haemorrhage	1 (3.6) 1	0	0	0	1 (0.5) 1
Infection and infestations	**0**	**1 (3.4) 1**	**2 (7.4) 2**	**0**	**3 (1.4) 3**
Catheter site infection	0	0	1 (3.7) 1	0	1 (0.5) 1
Gastroenteritis	0	0	1 (3.7) 1	0	1 (0.5) 1
Pyelonephritis	0	1 (3.4) 1	0	0	1 (0.5) 1
Injury, poisoning, and procedural complications	**1 (3.6) 1**	**1 (3.4) 1**	**0**	**1 (0.7) 2**	**3 (1.4) 4**
Accidental exposure to product	1 (3.6) 1	0	0	0	1 (0.5) 1
Incision site inflammation	0	0	0	1 (0.7) 1	1 (0.5) 1
Meniscus injury	0	1 (3.4) 1	0	0	1 (0.5) 1
Wound dehiscence	0	0	0	1 (0.7) 1	1 (0.5) 1
Musculoskeletal and connective tissue	**0**	**1 (3.4) 1**	**0**	**2 (1.5) 2**	**3 (1.4) 3**
Cervical spinal stenosis	0	0	0	1 (0.7) 1	1 (0.5) 1
Lumbar spinal stenosis	0	1 (3.4) 1	0	0	1 (0.5) 1
Systemic lupus erythematosus	0	0	0	1 (0.7) 1	1 (0.5) 1
Neoplasms benign, malignant and unspecified	**0**	**0**		**1 (0.7) 1**	**1 (0.5) 1**
Fibrosarcoma	0	0	0	1 (0.7) 1	1 (0.5) 1
Psychiatric disorders	**0**	**1 (3.4) 1**	**0**	**0**	**1 (0.5) 1**
Bipolar II disorder	0	1 (3.4) 1	0	0	1 (0.5) 1
Vascular disorders	**0**	**0**	**0**	**1 (0.7) 1**	**1 (0.5) 1**
Lymphoedema	0	0	0	1 (0.7) 1	1 (0.5) 1

m=number of events; n=number of subjects experiencing the event; q2wks=every 2 weeks; q4wks=every 4 weeks; RO=rollover (subjects); TEAE=treatment-emergent adverse events

Subjects were counted once per system-organ-class and once per preferred term.

Treatment-emergent adverse events are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.

In the lanadelumab treated population (n=220), 15 SAEs were reported in 11 subjects. There are small numbers in each group, no specific pattern can be found. It is noted that none of the SAEs was considered related to the study treatment.

Safety update

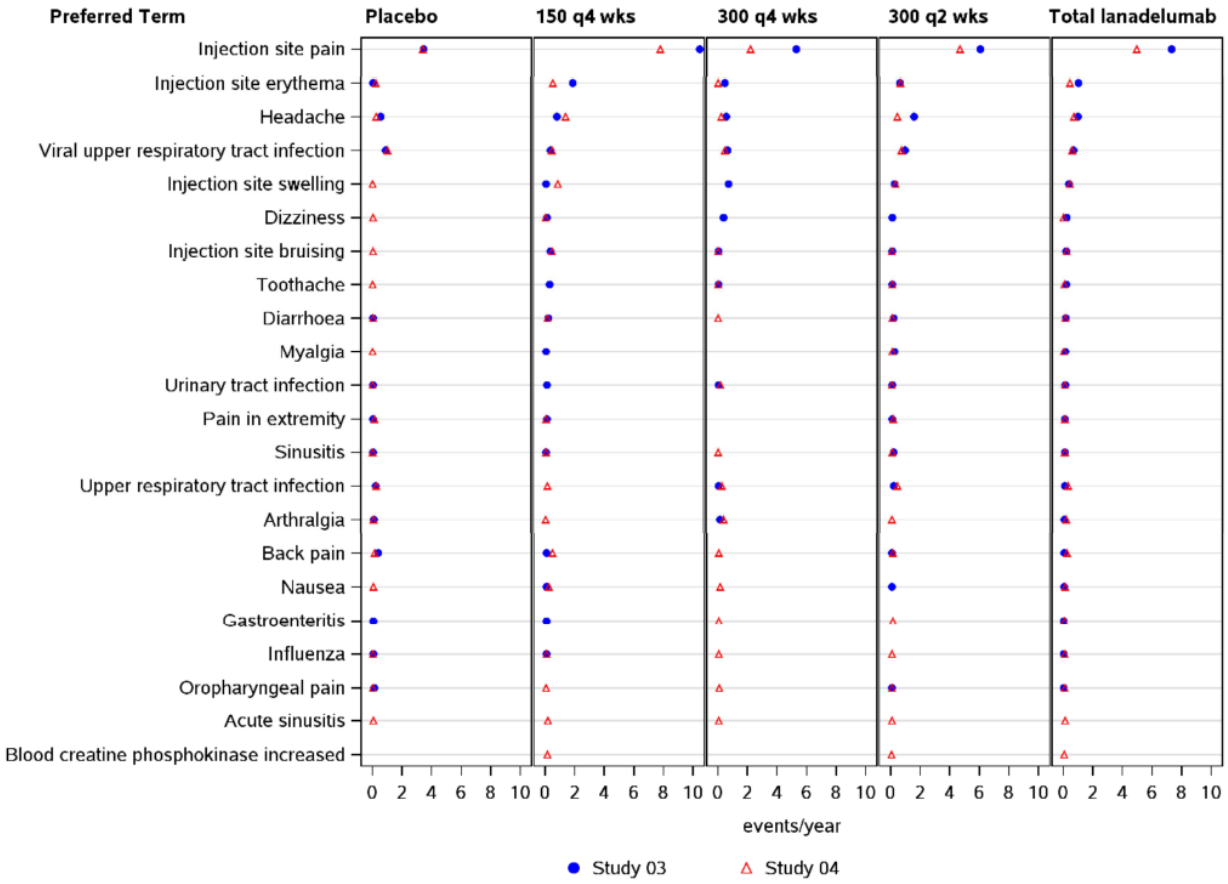
Since lanadelumab is intended for long-term use, it is of interest to know if the frequency of AEs changes over time. It is noted that the division of subjects into rollovers and non-rollovers do not directly translate to subjects with longer and shorter lanadelumab exposure. No placebo-controlled data is available after 6 months of treatment but open label extension study is ongoing. An updated summary of the safety profile of lanadelumab based on the 120 days safety update data cut on 01 Jan 2018 (4 months of additional information available from the ongoing Study DX-2930-04 since the initial filing) was provided during the assessment. See below.

Table 28 Comparing Treatment-emergent Adverse Event Rate Observed in Study DX-2930-03 Versus Study DX-2930-04 (Data Cut for 120 Days Safety Update)- Study DX-2930-03 Rollover Population

	Placebo		Pooled lanadelumab	
Event rate TEAE	**Study DX-2930-03 N=41**	**Study DX-2930-04 N=33**	**Study DX-2930-03 N=84**	**Study DX-2930-04 N=76**
Total subject time (years)	18.9	30.0	41.2	62.7
Mean subject time (years)	0.46	0.91	0.49	0.83
Any TEAE				
n	236	292	690	727
Incidence rate (events/year)	12.49	9.73	16.74	11.59
Any Related TEAE				
n	86	94	420	295
Incidence rate (events/year)	4.55	3.13	10.19	4.70
Any Severe TEAE				
n	7	6	10	8
Incidence rate (events/year)	0.37	0.20	0.24	0.13
Any Serious TEAE				
n	0	3	4	5
Incidence rate	0	0.10	0.10	0.08

Subjects were summarized by their treatment group during study DX-2930-03. 'Study 03' sub-columns contain adverse events occurred during the treatment period of study DX-2930-03; 'Study 04' sub-columns contain adverse events occurred during the 'Regular Dosing Stage' or within 14 days after the first dose of study DX-2930-04.

Figure 11 Event rates that occur in ⩾5% of the subjects by preferred term in descending order of frequency in Study DX-2930-03 and Study DX-2930-04 (Data Cut-120 Days Safety Update)-Rollover Population



A comparison of study DX-2930-03 and DX-2930-04 regarding incidence rates for the pooled lanadelumab treated population (Table 20) suggests that the incidence rates for TEAEs are not increasing over time. Moreover, no treatment-related SAEs or deaths were reported and no additional related severe TEAEs have been reported since the initial submission. There was no increase in SAEs or AESIs with longer term exposure to lanadelumab.

Figure 9 shows that common adverse events in the overall lanadelumab treated group are consistently overlapping between study DX-2930-03 compared to study DX-2930-04, with the exception of injection site pain, which tend to occur more often in the placebo controlled study. The rates of discontinuations are 6/84 in study DX-2930-03 compared to 7/76 in study DX-2930-04. AE reported as a reason for discontinuation concerns one patient in each study.

Altogether, data do not suggest that common adverse events or discontinuations would increase over time (and therefore be more common in the follow-up study).

Laboratory findings

Phase 3 Studies

Hematology

In study DX-2930-03, all subjects in the placebo arm and the pooled lanadelumab treatment arms had values in the normal range during the pre-treatment and the treatment periods.

In study DX-2930-04; a total of 3 subjects (1 rollover and 2 non-rollovers) shifted from normal to low values in neutrophils.

In study DX-2930-04, one subject reported five events, which was related to blood loss following surgery to remove a gluteal fibrosarcoma.

Coagulation

Background

There was a trend for slight increase in aPTT and other coagulation parameters for lanadelumab-treated subjects compared with placebo-treated subjects. Prolongation of aPTT is an expected on target effect of plasma kallikrein inhibition in the coagulation assay since aPTT reagents (kaolin, silica or ellagic acid or dextran sulfate) activate FXII to FXIIa, which then cleaves prekallikrein to generate plasma kallikrein. Plasma kallikrein, in turn, generates additional FXIIa, which converts FXI to FXIa to initiate coagulation via the intrinsic pathway (Wu, 2015).

In contrast to patients with severe prekallikrein deficiency, lanadelumab does not completely inhibit plasma kallikrein activity, as evidenced by cleaved high molecular weight kininogen (cHMWK) pharmacodynamic biomarker levels in plasma of lanadelumab treated HAE patients that approach that of healthy controls (Banerji et al., 2017). Deficiencies in either of the contact system proteins (FXII, HMWK, or prekallikrein), as well as FXI, are identified through a prolongation of the aPTT in the test (Silverberg et al., 1995). While a deficiency in FXI can be associated with impaired hemostasis (hemophilia C), severe deficiencies in the other three contact system proteins (FXII, HMWK, or prekallikrein) do not induce a bleeding tendency (Schmaier, 2016). A severe deficiency in prekallikrein leads to an aPTT that can be in excess of 100 seconds in the test, whereas the normal reference range for the assay is usually 25-40 seconds (Girolami et al., 2010; Silverberg et al., 1995). Despite the long aPTT, there is no increased risk of bleeding. Therefore, a prolonged aPTT due to plasma kallikrein inhibition is not predictive of impaired in vivo coagulation and not related to a bleeding risk.

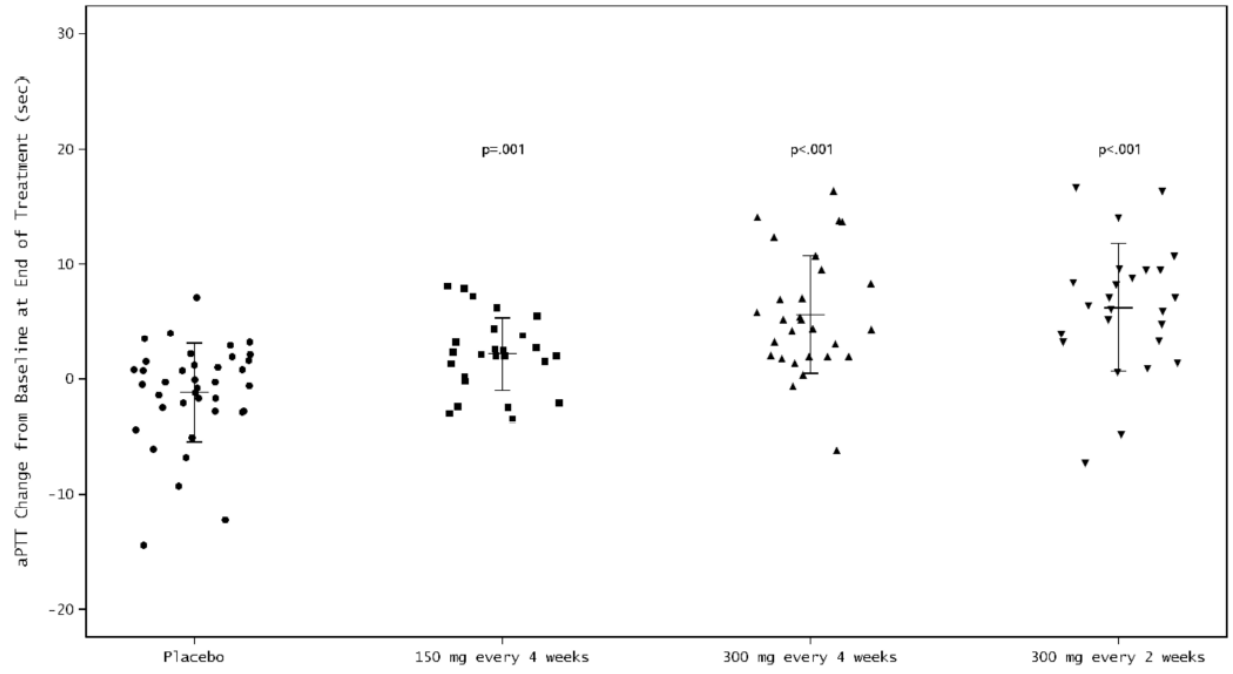
Table 29 Study DX-2930-03 Actual values and change from baseline in coagulation results (aPTT) by treatment group and study visit

Parameter Timepoint	Statistic	Placebo N=41	DX-2930 150 mg every 4 weeks N=28	DX-2930 300 mg every 4 weeks N=29	DX-2930 300 mg every 2 weeks N=27	DX-2930 Total N=84
Activated Partial Thromboplastin Time (sec)						
DAY 0 / WEEK 0	n	41	28	29	27	84
	Mean	28.38	28.21	28.46	28.61	28.43
	SD	3.835	3.013	4.066	5.465	4.232
	Median	27.00	28.00	28.70	27.30	28.20
	Min, Max	24.3, 40.5	22.2, 34.1	19.6, 37.2	20.0, 42.3	19.6, 42.3
DAY 28 / WEEK 4	n	39	27	29	26	82
	Mean	29.44	30.56	31.78	36.52	32.88
	SD	4.705	3.937	4.865	8.445	6.453
	Median	28.00	29.30	30.90	33.75	30.95
	Min, Max	24.1, 49.5	25.3, 38.9	24.7, 45.7	27.4, 54.9	24.7, 54.9
CHANGE FROM BASELINE TO DAY 28 / WEEK 4	n	39	27	29	26	82
	Mean	1.08	2.25	3.32	7.83	4.40
	SD	4.009	3.577	5.370	8.828	6.624
	Median	0.90	1.40	2.70	6.35	3.40
	Min, Max	-6.5, 15.4	-3.2, 11.1	-6.2, 18.5	-10.9, 28.7	-10.9, 28.7

DAY 182 / ET	n	38	26	28	25	79
	Mean	27.15	30.60	34.06	35.26	33.30
	SD	2.857	3.013	4.979	4.764	4.727
	Median	26.75	31.15	33.05	35.10	32.80
	Min, Max	21.4, 33.9	25.5, 35.3	27.0, 46.8	26.9, 44.3	25.5, 46.8
CHANGE FROM BASELINE TO DAY 182 / ET	n	38	26	28	25	79
	Mean	-1.18	2.17	5.61	6.22	4.67
	SD	4.314	3.229	5.180	5.603	5.045
	Median	-0.40	2.20	4.80	6.40	4.20
	Min, Max	-14.5, 7.1	-3.5, 8.1	-6.2, 16.3	-7.3, 16.6	-7.3, 16.6

Figure 12

. Change in Activated Partial Thromboplastin Time from Baseline to End of Treatment by Treatment Group in Study DX-293003-(Safety Population*



*The horizontal lines represent mean ± standard deviation. The p values were based on t-test comparing each lanadelumab group to the placebo group.

In study DX-2930-03, aPTT is well balanced between groups at baseline, day 0. Changes from baseline are in line with what can be predicted from primary pharmacology with increases in aPTT. The increase in aPTT seems dose-dependent and changes appear from the first measurement after study start, i.e. day 28. These changes are then maintained throughout the study period up to day 182.

In study DX-2930-04 aPTT was monitored and the change from baseline is shown to be elevated, at most 5.71 seconds at day 224 on group level. For the individual subject with the largest increase, aPTT was increased 86.9 s. The actual value was 120.5 s, at day 56. The increases in aPTT do not seem to increase with time.

Table 30 Study DX-2930-03 Shift table of highest coagulation by treatment group

Parameter Posttreatment	Placebo (N=41)		Lanadelumab Total (N=84)	
	Pretreatment		Pretreatment	
	≤1.5 x ULN n (%)	>1.5 x ULN n (%)	≤1.5 x ULN n (%)	>1.5 x ULN n (%)
Activated Partial Thromboplastin Time (sec)				
≤1.5 x ULN	41 (100.0)	0	83 (98.8)	0
>1.5 x ULN	0	0	1 (1.2)	0
Prothrombin International Normalized Ratio				
≤2 x ULN	41 (100.0)	0	84 (100.0)	0
>2 x ULN	0	0	0	0
Prothromin Time (sec)				
≤1.5 x ULN	37 (90.2)	1 (2.4)	79 (94.0)	0
>1.5 x ULN	3 (7.3)	0	5 (6.0)	0

Sec=second; ULN= upper limit of normal

Increases are according to the applicant small and 83/84 lanadelumab treated subjects had aPTT <1.5 x ULN. In study DX-2930-03, prothrombin international normalized ratio and prothrombin time are balanced between groups. No bleeding events were observed in association with a prolonged aPTT, and no effects on PT, INR were observed in subjects treated with lanadelumab. It is therefore agreed that increases in aPTT are not considered related to an increased risk of bleeding and that the observed aPTT prolongations are therefore not clinically relevant.

Overall, presented findings are supportive of the view that increased aPTT levels can be considered as laboratory finding consistent with the mechanism of action.

Liver-related Biochemical Tests

Some lanadelumab treated subjects were noted to have transient asymptomatic elevations in ALAT to >3x ULN during study DX-2930-03. The clinical picture in these subjects was generally one of extensive comorbidities including prior liver disease such as hepatic steatosis or presumed non-alcoholic fatty liver disease, hepatic adenoma resection, metabolic syndrome, obesity, and/or prior hepatotoxic drug use (eg, danazol).

Study DX-2930-03

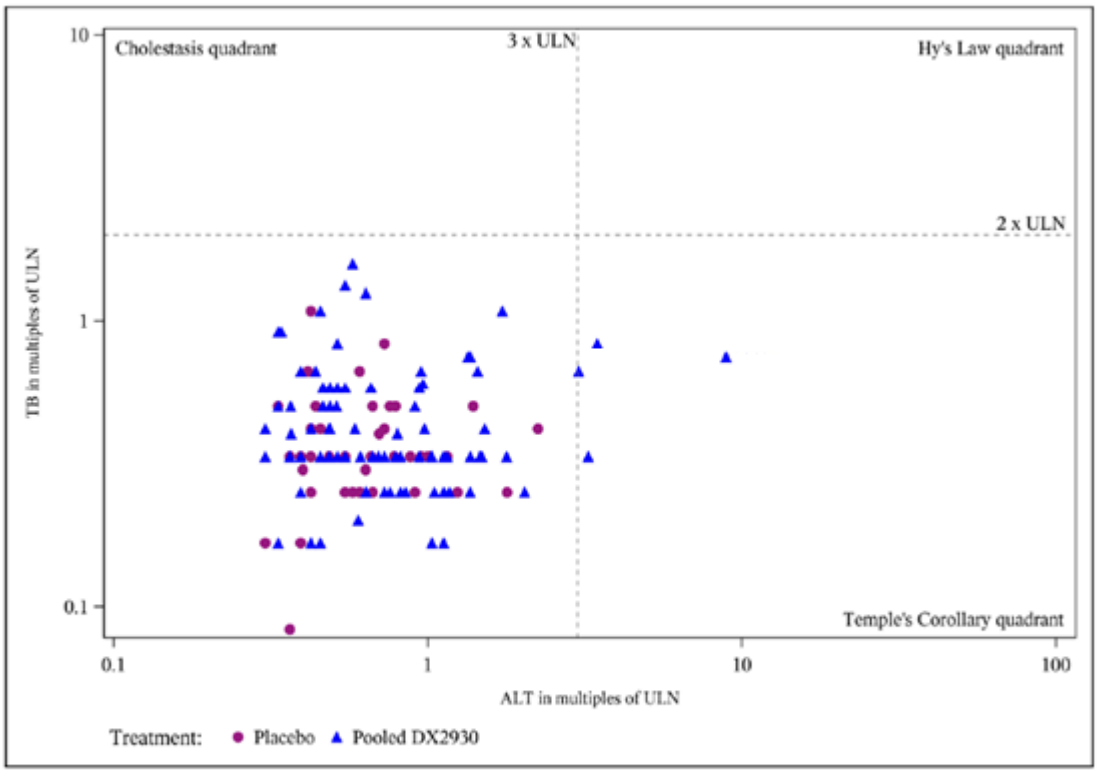
Table 31 actual values and change from baseline in chemistry (ALAT) results by treatment group and study visit

Parameter Timepoint	Statistic	Placebo N=41	DX-2930 150 mg every 4 weeks N=28	DX-2930 300 mg every 4 weeks N=29	DX-2930 300 mg every 2 weeks N=27	DX-2930 Total N=84
Alanine Aminotransferase (U/L)						
DAY 0 / WEEK 0	n	41	28	29	27	84
	Mean	18.3	21.8	22.5	31.9	25.3
	SD	7.59	12.53	14.86	20.31	16.61
	Median	17.0	17.0	17.0	26.0	18.5
	Min, Max	10, 49	9, 51	12, 80	10, 76	9, 80
DAY 28 / WEEK 4	n	39	26	28	24	78
	Mean	20.1	29.8	19.6	27.3	25.4
	SD	13.24	54.91	13.40	16.61	33.83
	Median	16.0	17.5	16.0	19.5	18.0
	Min, Max	10, 74	6, 294	6, 66	5, 73	5, 294
CHANGE FROM BASELINE TO DAY 28 / WEEK 4	n	39	26	28	24	78
	Mean	1.6	8.2	-2.9	-3.3	0.7
	SD	11.69	49.28	6.31	14.56	29.90
	Median	0.0	0.0	-2.0	-2.5	-1.0
	Min, Max	-28, 50	-24, 247	-22, 10	-50, 24	-50, 247
DAY 182 / ET	n	38	26	28	25	79
	Mean	18.1	18.0	24.5	25.8	22.8
	SD	9.52	10.34	26.72	15.44	19.14
	Median	16.0	15.0	16.5	21.0	17.0
	Min, Max	8, 52	6, 50	9, 140	8, 68	6, 140
CHANGE FROM BASELINE TO DAY 182 / ET	n	38	26	28	25	79
	Mean	0.1	-2.2	1.7	-5.9	-2.0
	SD	7.85	8.74	19.70	22.95	18.19
	Median	-0.5	-1.0	-2.0	-1.0	-2.0
	Min, Max	-32, 19	-31, 14	-26, 93	-62, 47	-62, 93

ALAT levels are markedly higher at baseline in the lanadelumab 300 mg every 2 weeks treated group and also higher in the overall lanadelumab treated groups. ALAT levels do not increase in lanadelumab treated groups during the 6-month study period.

An ad hoc analysis evaluating drug-induced serious hepatotoxicity (eDISH plot), study DX-2930-03

Figure 13



Abbreviations: ALT=alanine aminotransferase; DX-2930=lanadelumab; TB=total bilirubin; ULN=upper limit of normal

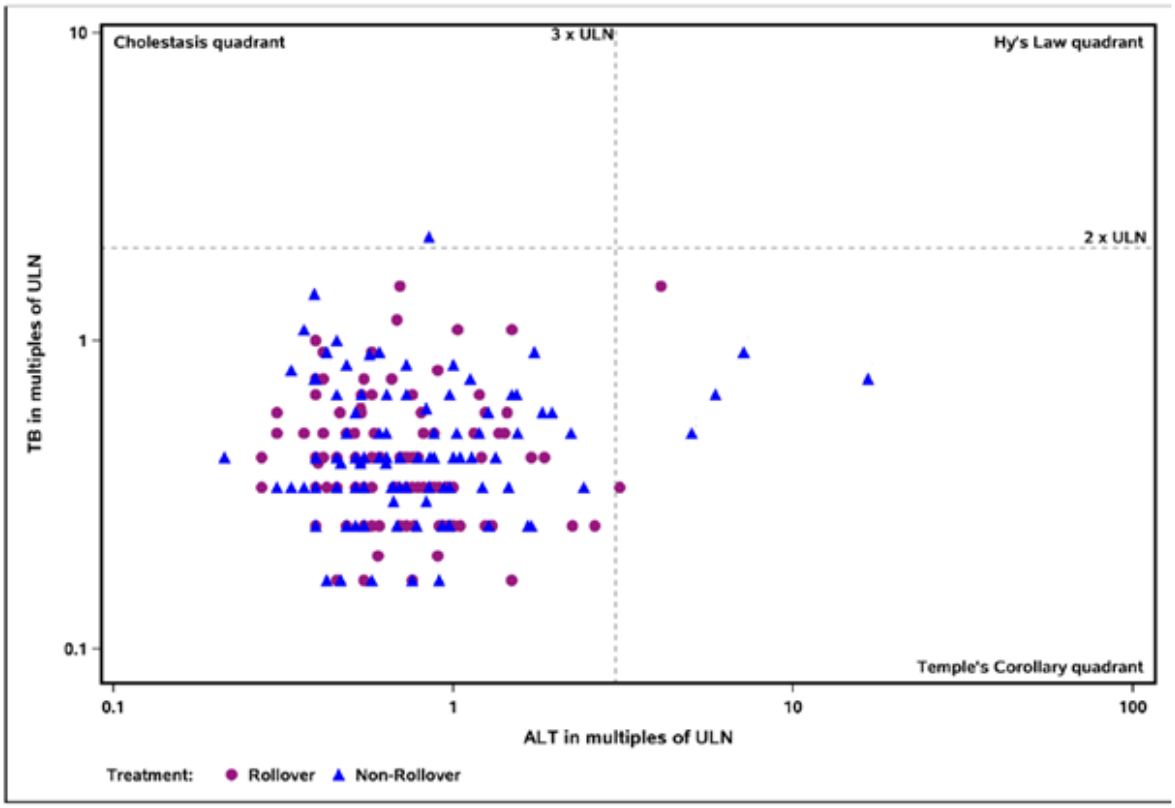
Source: Module 5.3.5.1, DX-2930-03 CSR, Figure r2609.5.

In the placebo controlled study DX-2930-03 four lanadelumab treated subjects and zero placebo treated subjects had elevated ALAT >3X ULN during the study.

Study DX-2930-04

6 subjects had peak ALT >3×ULN regardless of baseline ALT level (4 normal at baseline and 2 elevated at baseline; 2 rollovers and 4 nonrollovers) and 1 subject (nonrollover) with a peak total bilirubin >2×ULN (mildly elevated at baseline).

Figure 14 An ad hoc analysis evaluating drug-induced serious hepatotoxicity (eDISH plot), study DX-2930-04



Abbreviations: ALT=alanine aminotransferase; DX-2930=lanadelumab; TB=total bilirubin; ULN=upper limit of normal

Pooled phase 3 study experience

Elevated ALT >3X ULN (regardless of baseline - with up to 3X allowed) was reported in 10 of 233 subjects (4.3%)

All 10 subjects (4 in study DX-2930-03, 6 in study DX-2930-04) with elevations were asymptomatic, with no associated hyperbilirubinemia (no Hy's Law cases) or elevated alkaline phosphatase (ALP)

5/10 returned to baseline while lanadelumab was continued (with drug tolerance/adaptation in evidence)

2 subjects had an intentional rechallenge (and both were negative)

2 subjects discontinued at the discretion of investigator - with no sequelae

1 subject was paused and is undergoing further evaluation

Summary points

- Asymptomatic, reversible, mild-moderate ALT/AST elevations with a latency of 1-6 months; the incidence appears to be <5% of subjects

- Evidence for drug tolerance (adaptation) is apparent and seems to be the most common course

- No signs of hypersensitivity reactions

- No Hy's Law cases or cases of acute liver failure

- No grade 4 ALT/AST elevations

- Negative rechallenge responses have been seen when lanadelumab has been paused and restarted

- No correlation of ALT/AST elevations to plasma concentrations

- No antidrug antibody formation for all 10 subjects

One patient discontinued lanadelumab treatment due to elevated transaminases and the transaminases fell after treatment discontinuation, which could be interpreted as a positive dechallenge. It is concurred that 2/4 patients had pre-existing liver disease (hepatic steatosis).

There is currently insufficient evidence to suggest that individuals with chronic liver disease and cirrhosis are at increased risk of drug induced liver injury while on lanadelumab. Patients with AT elevations can thus be given lanadelumab.

It can be concurred that metabolism of proteins (e.g. lanadelumab) generally does not generate toxic intermediates and, therefore, monoclonal antibodies are unlikely to induce drug induced liver injury via production of toxic metabolites. It is argued by the applicant that hepatotoxicity has not been identified as a general safety concern with therapeutic monoclonal antibodies as a class. However, there are examples of licensed monoclonal antibodies with elevated aminotransferases as common adverse reactions.

Overall, it is plausible to attribute some of the observed enzyme elevations to lanadelumab treatment and it is agreed that such transaminase elevations could currently be regarded as idiosyncratic. However, it is still considered unknown whether lanadelumab could potentially be linked with more pronounced transaminase elevations in a larger treatment population. Cases of jaundice and hepatitis have for example been observed in the post-marketing experience for other monoclonal antibodies.

Other clinical chemistry parameters

In study DX-2930-03, all subjects in the placebo arm and the pooled lanadelumab treatment arms had values in the normal range during the pretreatment and the treatment periods for chemistry parameters of glucose, potassium, and urea nitrogen.

Creatinine level

In study DX-2930-03, on group level there were no increases in creatinine observed in the lanadelumab treated population. 2/27 (7.4%) subjects in the lanadelumab 300 mg q2wks arm had creatinine value >1.5 x ULN during the pretreatment period. For 1 subject, the creatinine level was normal during the treatment period, while the creatinine level for the other subject remained elevated at >1.5 x ULN during the treatment period. A shift from pretreatment period normal value (≤1.5 x ULN) to a higher value (>1.5 x ULN) was observed for creatinine (mg/dL) in 1/29 (3.4%) subjects in the lanadelumab 300 mg q4wks treatment arm.

Electrocardiogram findings

In studies DX-2930-03, DX-2930-04 and in the phase 1 studies, according to the applicant, no clinically significant ECG abnormality, e.g QTc prolongation or QRS widened complexes was observed in any subject.

Vital signs

In studies DX-2930-03, DX-2930-04 and in the phase 1 studies, according to the applicant, there were no important safety signals identified in terms of mean changes from baseline or categorical shifts from normal to abnormal in vital sign results.

Adverse events of special interest (AESIs)

Hypersensitivity

Monoclonal antibodies are known to cause hypersensitivity reactions (Kleyman and Weintraub, 2012), that include injection site reactions (Corominas et al., 2014).

No anaphylaxis or anaphylactoid events were reported in the phase 3 studies.

Some AESIs were reported by the specific preferred term of "hypersensitivity", while other events were reported as "injection site reactions" but identified as an AESI by the Investigator. Both types of events are described in the following sections of "hypersensitivity".

Study DX-2930-03
Three lanadelumab-treated subjects had a total of 5 related events (all mild in severity) that were investigator-defined AESI, with the preferred terms of injection site reaction, erythema, or induration.

In the lanadelumab 300 mg q2wks treatment arm, 1 subject had 2 related events reported as hypersensitivity reactions (1 mild and 1 moderate in severity), which included symptoms of tingling, itchiness, and discomfort of the tongue, dry cough, and mild headache.

None of the 4 subjects received any concomitant treatment for the AESI of hypersensitivity; they completed the study without any further symptoms and rolled over into Study DX-2930-04.

No subject in the placebo group experienced an investigator-defined AESI of hypersensitivity.

Study DX-2930-04
There were 7 investigator-reported hypersensitivity AESIs in 6 subjects. One AESI of hypersensitivity was classified as related and severe. It coincided with an HAE attack. Three subjects discontinued lanadelumab to AESIs of hypersensitivity reactions (2 subjects) or injection site papule (1 subject).

Overall, hypersensitivity reactions are adequately described and considered as identified risk in the lanadelumab treated population. It is noted that there are so far no anaphylactic reactions reported in the study population.

Disordered coagulation (hypercoagulability events and bleeding events)

Study DX-2930-03
A total of 17 (20%) of lanadelumab-treated subjects had 32 events and 6 (15%) placebo-treated subjects had 14 events of SMQ-defined bleeding, predominantly related to the injection site.

23 events in 9 subjects (3 subjects in each lanadelumab treatment arm) were considered related to lanadelumab administration (injection site bruising, injection site hemorrhage, and injection site hematoma). Eight events in 2 placebo-treated subjects were considered related SMQ-defined events of bleeding.

One subject diagnosed with gastroesophageal reflux had mild microcytic anemia, although screening hemoglobin and hematocrit were below the normal range and there was no actual event of "bleeding" reported.

There were no treatment-emergent events of SMQ-defined hypercoagulation during the treatment period. There was no apparent excess of treatment emergent cardiovascular adverse events in any of the DX-2930 treatment groups.

Study DX-2930-04
There were 2 subjects with 4 AESIs of disordered coagulation. All 4 events related to abnormal vaginal bleeding. One subject had experienced a hormonal change with oral contraceptive (norethindrone), and this product had

the listed side effects of “vaginal bleeding between periods”. The other subject had a comorbid history of uterine adenomyosis, which was treated surgically, and resolved without incident. None of the events were related, serious or required discontinuation of treatment. One of the 2 subjects with AESI events of vaginal haemorrhage had an ADA-positive sample. The presence of ADA was not temporally related to the AESI, as the bleeding events were reported approximately 3 months prior to the low titer ADA-positive sample.

Injection-site reaction (ISR)

ISR AEs were not predefined in the protocols but were identified as AEs with the PTs starting with ‘Injection site,’ ‘Application site,’ or ‘Administration site.’ Most ISRs were considered related to treatment. No subject treated with lanadelumab reported an ISR that was serious or severe. 97% of ISRs were mild intensity (3% were moderate), and 90% of all ISRs resolved within 1 day of onset with a median duration of 6 minutes.

In study DX-2930-03, ISRs are much more common in the lanadelumab treated group compared to placebo (injection site pain 43% vs 29%, injection site erythema 9.5% vs 2.4%, injection site bruising, 7.1% vs 0%).

In study DX-2930-04 when assessing ISRs by administration type and anatomical location, injections given in thigh had more ISRs per dose than those given in the arm or abdomen for self and study staff administrations (eg, 1.232, 0.068, and 0.233, respectively, for self-administration at home. It should be noted that the fewest doses were administered in the thigh. Injections given in the arm had the fewest ISRs per dose, although this site was not the preferred location for subjects self-administering. The majority of self-administered doses were given in the abdomen and the event rates of ISRs for self-administered doses versus study staff administrations in the abdomen were comparable. Regardless of administration type, the majority of ISRs were ≤0.5 hour duration, with 81% to 92% of all injection-site reaction AEs ≤1 day in duration across the 3 administration site categories.

Pooled data for DX-2930-03 and DX 2930-04 (n=220)

In terms of the number of events reported, ISRs were the most frequently reported TEAEs with 1190 AEs reported by 53% of lanadelumab-treated population.

97% of ISRs were mild intensity and 90% of all ISRs resolved within 1 day of onset. Injection site reactions occur to a similar extent from self-administration of lanadelumab.

Safety in special populations

Paediatric population

Table 32 Summary of treatment emergent adverse events (excluding HAE attack reported events) for the pediatric population (n=23)

Summary of Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events) by BMI Group
(Lanadelumab-treated Population)

	BMI category: Other - Pediatrics (N=23)									
	150mg Q4w - 300mg Q2w (N=1)		300mg Q4w - 300mg Q2w (N=3)		300mg Q2w - 300mg Q2w (N=2)		Placebo ROs + DX-2930-04 NROs (N=17)		Lanadelumab-treated Population (N=23)	
Category	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Overall Subject-time (years)	0.5		3.4		2.3		10.7		17.0	
Average Subject-time (years)	0.54		1.14		1.17		0.63		0.74	
Total Number of Doses	13		82		56		286		437	
Average Number of Doses	13.0		27.3		28.0		16.8		19.0	
Any TEAE	1 (100.0)	3	3 (100.0)	8	2 (100.0)	57	14 (82.4)	72	20 (87.0)	140
Any Related TEAE	1 (100.0)	1	1 (33.3)	2	2 (100.0)	41	7 (41.2)	50	11 (47.8)	94
Any Serious TEAE	0	0	0	0	1 (50.0)	1	0	0	1 (4.3)	1
Any Related Serious TEAE	0	0	0	0	0	0	0	0	0	0
Any Severe TEAE	0	0	0	0	1 (50.0)	1	0	0	1 (4.3)	1
Any Related Severe TEAE	0	0	0	0	0	0	0	0	0	0
Any Investigator-reported AESI	0	0	0	0	0	0	0	0	0	0
Deaths due to TEAE	0	-	0	-	0	-	0	-	0	-
Hospitalizations due to TEAE	0	0	0	0	1 (50.0)	1	0	0	1 (4.3)	1
Discontinuation due to TEAE	0	-	0	-	0	-	0	-	0	-

The 23 subjects (⩾12 to <18 years) received a total of 413 doses of lanadelumab (150 or 300 mg).
In total, 23 paediatric subjects (aged 12 to <18 years) have participated across the 2 Phase 3 studies as of 01 Sep 2017.

No relevant differences between the TEAE profile for paediatric subjects and that reported for adult subjects were identified. The most frequently reported treatment-related TEAE was injection site pain. No paediatric subjects had reported investigator-confirmed AESIs in Study DX-2930-03 or until the interim analysis data cut of 01 Sep 2017 in Study DX-2930-04.

One paediatric subject in the lanadelumab treatment arms in Study DX-2930-03 had 1 unrelated severe, serious TEAE of catheter site infection. There were no deaths or discontinuations in paediatric subjects due to TEAEs during the treatment period in either of the Phase 3 studies.

Across the two Phase 3 studies 1 paediatric rollover subject was positive for ADA classified as neutralizing with no apparent clinical consequence.

There were no safety signals identified in terms of clinical laboratory hematology or coagulation, laboratory test abnormalities, vital signs, physical examination or ECGs. No subject had ALAT, ASAT or ALP elevation in the range of >3 x ULN posttreatment. Liver biochemistry abnormalities were observed in 1-<3 x ULN range pretreatment (baseline) in both Phase 3 studies; however, no shifts in these values posttreatment were observed. One paediatric nonrollover subject in Study DX-2930-04 had a shift in ALP values from normal to 1-<3 x ULN posttreatment.

No firm conclusions can be drawn from the relatively few (n=23) patients in the adolescent population. On the other hand, current findings do not suggest an increased risk.

Elderly population

Elderly subjects (>65 to 76 years, N=10) were included in the clinical package. Among those subjects, one subject was not included in the PK/PD dataset due to inconsistent PK profile; and 2 subjects turned >65 years old in Study DX-2930-04. The results suggested no difference in the PK properties and exposure of lanadelumab between elderly and adult subjects. Furthermore, in the post-hoc PK analysis, no influence of age was apparent on the CL/F and Vc/F of lanadelumab after correcting for body weight, which supports that no difference in the PK properties and exposure of lanadelumab are expected for elderly subjects with HAE (>65 to 76 years) although no clinical data are available.

In addition, in the pivotal DX-2930-03 study, all three dose regimens of lanadelumab were generally well tolerated over the 26-week treatment period. No discernible dose-response pattern or dose-dependent or limiting toxicity was observed for any related TEAE. Also, no relationship between the exposure of lanadelumab and safety endpoints of interest were identified, which includes laboratory parameters, vital signs and ECG assessments. Therefore, there are no safety concerns for elder HAE patients even if they have a larger variation of lanadelumab exposure.

Overall no safety warningis warranted in elderly HAE patients. Long-term safety in the adult population is included in the Safety specification as Missing information in the RMP.

Hepatic insufficiency

No dedicated study has been conducted in subjects with hepatic impairment.

In study DX-2930-03, exclusion criteria included alanine aminotransferase (ALT) >3x upper limit of normal, or aspartate aminotransferase (AST) >3x upper limit of normal, or total bilirubin >2x upper limit of normal (unless the bilirubin elevation is a result of Gilbert's syndrome).

The applicant has not found a mechanistic rationale that lanadelumab would affect liver function and there is generally insufficient evidence to suggest that patients with liver disease are systematically predisposed to DILI. Therefore it is considered that HAE patients with mild/moderate/severe hepatic insufficiency can be treated with lanadelumab and no safety precaution is warranted in these patients.

Renal insufficiency

No dedicated study has been conducted in subjects with renal impairment.

As currently assessed in the Pharmacokinetic AR, renal impairment is not expected to affect exposure to lanadelumab. No dose adjustment is required in patients with renal impairment. Presented data do not suggest that PK/PD is different in subjects with mild–moderate renal impairment. No subject included in the Phase 3 studies had severe renal impairment. Twelve subjects in phase 3 studies had moderate renal impairment (eGFR 30-59 ml/min/1.73m2). 114 subjects had mild renal impairment (eGFR 60-89 mL/min/1.73m2) and 102 subjects had normal kidney function (eGFR ≥90 ml/min/1.73m2).

It is agreed that the presented safety findings, stratified for kidney function, do not imply that subjects with mild to moderate renal impairment are at an increased risk for ADRs.

Pregnancy and lactation

Pregnancy

Background

Lanadelumab, was engineered to specifically bind and inhibit pKal without binding prekallikrein (Kenniston et al., 2014). As a result of this specificity, lanadelumab does not completely suppress pKal activity or bradykinin

generation. This mechanism of action of lanadelumab allows for basal level pKal activity to persist and thus is not expected to fully inhibit contact system activation in newborns.

In contrast to the regulation of excess pKal activity observed in lanadelumab-treated subjects, individuals with homozygous deficiency in prekallikrein are completely devoid of plasma kallikrein activity (Girolami et al., 2010). Despite lacking pKal activity, patients with prekallikrein deficiency have been described as having a prognosis similar to age-matched individuals and have no indication of clinically relevant adverse effects due to the absence of plasma kallikrein activity (Girolami et al., 2010). The benign clinical presentation of homozygous prekallikrein deficiency does not suggest any particular safety risks for the newborn due to a complete lack of pKal (Girolami et al., 2010).

Lanadelumab does not inhibit tissue kallikrein 1 (KLK1), a kinin generating protease distinct from plasma kallikrein (Kenniston et al., 2014). Consequently, lanadelumab is not expected to interfere with kinin generation by KLK1, which is widely expressed by many tissues and supports normal kinin physiology (Campbell, 2016). While a physiological role for the plasma kallikrein-kinin system in newborn development has not been established, kinins have been implicated in the regulation of vascular tone and bradykinin levels in newborn cord blood have been shown to be higher than blood levels in adults (Melmon et al., 1968). It has been hypothesized that bradykinin may constrict smooth muscle of the ductus arteriosus after birth and reduce blood flow as it narrows and then completely closes (Melmon et al., 1968). However, complete bradykinin B2 receptor blockade did not affect the pulmonary vasodilatory response caused by oxygen in near term fetal lambs, indicating that bradykinin release is not critical for oxygen-mediated pulmonary vasodilation (Banerjee et al., 1994). In the ePPND study conducted in cynomolgus monkeys with lanadelumab, closure of the ductus arteriosus was considered normal for infants at or near the day of parturition.

In experimental studies there was no treatment-related effect on pregnancy, parturition, embryo-fetal development, as well as survival, growth, and postnatal development of offspring evaluated for up to 3 months of age.

Data from clinical trials with lanadelumab

In the Phase 3 clinical studies with lanadelumab, 3 pregnancies were reported, as of the interim data cut date of 01 Sep 2017, and the newborns (4, including twins) delivered to date are healthy. Since the subjects discontinued treatment soon after pregnancy was reported, the level of lanadelumab exposure to the fetus in the third trimester is minimal.

One Subject had a premature delivery of a healthy infant girl at 36 weeks of gestation. Following confirmation of pregnancy, lanadelumab treatment was stopped and the subject was followed up for safety to collect information on adverse events and concomitant medications. The subject experienced the following adverse events during her pregnancy: nausea associated with pregnancy, intermittent dizziness, rash, HAE attack, elevated blood pressure, intermittent bilateral forearm pain, and preeclampsia. The subject returned to treatment (300 mg every 2 weeks) on June 20, 2018.

Another subject had a premature delivery of healthy infant boy and girl twins at 31 weeks gestation. Following confirmation of pregnancy, lanadelumab treatment was stopped, and the subject was followed up to collect safety information on adverse events and concomitant medications. The subject experienced the following adverse events during her pregnancy: nausea associated with pregnancy, gestational diabetes, and HAE attacks. The subject returned to treatment (300 mg every 2 weeks) on June 13, 2018.The 3 subjects entered Study DX-2930-04 as rollover subjects from Study DX-2930-03 and they all discontinued treatment with lanadelumab upon receipt of positive serum/urine pregnancy test. The cumulative lanadelumab exposure in the 3 subjects before discontinuation was 2400 mg, 6150 mg, 6750 mg.

The applicant will continue to monitor pregnancy outcomes in the ongoing long term safety study and collect pregnancy-related safety information through routine pharmacovigilance activities as mentioned in the RMP.

Based on the pharmacological mode of action, lack of preclinical signal and benign course in the three pregnancies reported so far, inclusion of “Use in Pregnancy" as missing information is recommended.

In conclusion, lanadelumab is recommended not to be used during pregnancy.

Lactation

Lanadelumab has not been studied in lactating females. It is not known whether lanadelumab is present in human milk; however it is known that IgGs are excreted in human milk. It is unknown if lanadelumab’s kinetic is similar to human IgGs and is decreasing to low concentrations soon few days after birth.

Subjects with weight <50 kg

Weight was shown to be a significant covariate for lanadelumab, i.e. low-weight patients are predicted to have a lower exposure than the average 70 kg patient.

In total, 7 subjects <50 kg were treated with lanadelumab in the two phase 3 studies. In study DX-2930-03, two subjects <50 kg were treated with placebo and one subject with lanadelumab 300 mg q4w. All three subjects rolled over to study DX-2930-04 and were treated with lanadelumab 300 mg q2w.

In study DX-2930-03, 2 TEAEs were reported by the lanadelumab treated subject and non by the placebo subjects. None of the TEAEs was considered related to treatment and none was serious or severe. Table 33 summarises the TEAE by weight class in study DX-2930-04.

Table 33 Summary of Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) during the Treatment Period by Weight Group (Safety Population) (DX-2930-04)

	<50 kg N=7	50-<75 kg N=95	75-<100 kg N=71	>100kg N=39
Any TEAE n (%) m	6 (85.7) 72	82 (86.3) 763	58 (81.7) 467	36 (92.3) 229
Related TEAE n (%) m	3 (42.9) 67	47 (49.5) 335	24 (33.8) 206	15 (38.5) 106
Total subject time (years)	4.7	61.2	43.2	24.4

Related TEAE (events) /subject year	14.2	5.5	4.8	4.3

n = Number of subjects experiencing the event, m = Number of events.

The rate of related TEAEs/ subject year was higher in the <50 kg subgroup compared to other subgroups. It is however noted that in the <50 kg subgroup, 3 subjects reported 67 related TEAEs, i.e. 93% of all reported TEAEs in this subgroup. No AESI or serious or severe AE were reported in subjects <50 kg.

Table 34 TEAEs (Excluding HAE Attack Reported Events) during the Treatment Period by Weight Group, System Organ Class and Preferred Term (Safety Population) (DX-2930-04)

Weight Category: <50 kg (N=7)								
System Organ Class Preferred Term	Rollover Subjects N=3			Non-Rollover Subjects N=4			Total N=7	
	n	(%)	m	n	(%)	m	n	(%)	m
Any TEAE	2	(66.7)	2	4	(100.0)	70	6	(85.7)	72
Gastrointestinal disorders	1	(33.3)	1	1	(25.0)	1	2	(28.6)	2
Abdominal pain	1	(33.3)	1	0	(0.0)	0	1	(14.3)	1
Constipation	0	(0.0)	0	1	(25.0)	1	1	(14.3)	1
General disorders and administration site conditions	0	(0.0)	0	4	(100.0)	68	4	(57.1)	68
Injection site pain	0	(0.0)	0	3	(75.0)	44	3	(42.9)	44
Injection site bruising	0	(0.0)	0	2	(50.0)	20	2	(28.6)	20
Injection site pruritus	0	(0.0)	0	1	(25.0)	1	1	(14.3)	1
Injection site swelling	0	(0.0)	0	1	(25.0)	3	1	(14.3)	3
Immune system disorders	0	(0.0)	0	1	(25.0)	1	1	(14.3)	1
Drug hypersensitivity	0	(0.0)	0	1	(25.0)	1	1	(14.3)	1
Infections and infestations	1	(33.3)	1	0	(0.0)	0	1	(14.3)	1
Influenza	1	(33.3)	1	0	(0.0)	0	1	(14.3)	1

n = Number of subjects experiencing the event, m = Number of events.

In study DX-2930-04, 68/72 (94.4%) of all TEAE and 67/67 (100%) of all related TEAEs in the <50 kg subgroup were injection site reactions. One event of drug hypersensitivity was reported, but was not deemed as related.

Overweight and obese subjects

In the integrated analyses, a trend was observed in the highest weight category (≥100 kg) that the proportion of subjects with severe TEAEs (17% vs 12%), related severe TEAEs (4.9% vs 1.8%), and discontinuations (7.3% vs 2.7%) was higher than the overall lanadelumab-treated population.

Review of overall TEAEs by system-organ- class (SOC) and PT showed that the proportion of subjects reporting TEAEs under the Investigations SOC was notably higher in subjects ≥100 kg (24%) compared with the overall lanadelumab-treated population (11%). Events of increased ALAT, increased ASAT, and increased creatine phosphokinase were the most frequent TEAEs in the Investigations SOC.

According to the applicant, comorbidities in these subjects may be contributing to the observed difference in TEAEs reporting rather than a reflection of lanadelumab treatment.

It is acknowledged that there was a baseline imbalance in weight and BMI in study DX-2930-03, with a higher proportion of heavy subjects in the lanadelumab group. Obese subjects constitute 30% of patients in study DX-2930-04 and safety findings indicate that overweight subjects could be more prone to experience AEs.

Immunological events

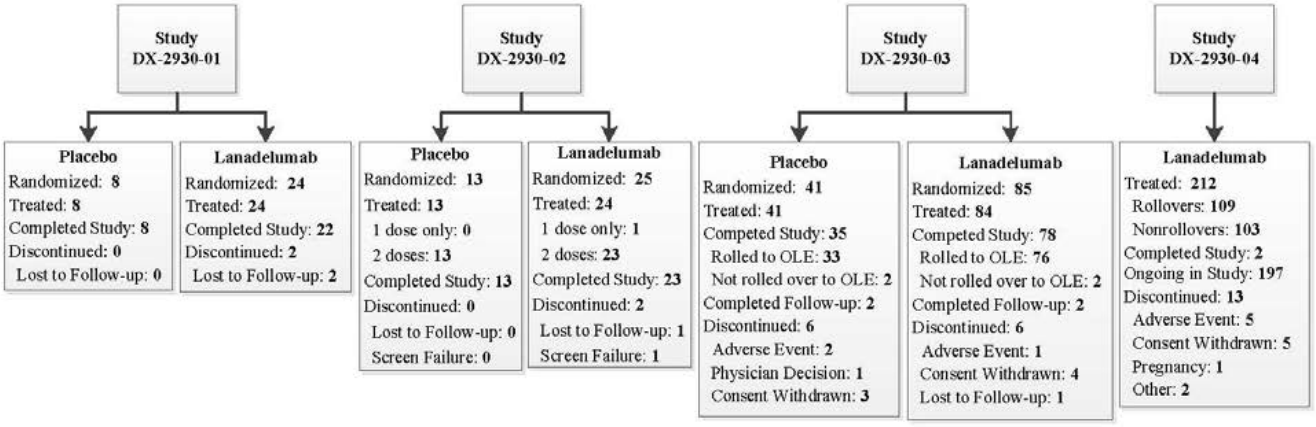
The overall prevalence of ADAs is under 12% in lanadelumab treated subjects. Pre-existing ADA positivity is 1.4%. None of the subjects with hypersensitivity AESIs developed ADAs. There is no hypersensitivity safety findings related to ADA positivity.

Safety related to drug-drug interactions and other interactions

No drug interaction studies were performed in this clinical program.

Lanadelumab is a monoclonal antibody. Interactions with other drugs are not anticipated due to the nature and metabolism of lanadelumab.

Discontinuation due to AES



DX-2930-03

Adverse events leading to discontinuations in the study (n=3) were due to a laryngeal HAE attack in the lanadelumab group and HAE attack and tension headache in the placebo group.

In DX-2930-04, discontinuations occur to the same extent in lanadelumab and placebo treated subjects in study DX-2930-03. In DX-2930-04, hypersensitivity reactions accounts for three out of five discontinuations due to adverse events.

Overall, 8 subjects discontinued study treatment due to AEs. In 4/6 lanadelumab-treated subjects, the TEAEs were considered related (ISRs, hepatic disorders and hypersensitivity).

Safety in phase 1 studies

Study DX-2930-01, single ascending dose

The highest tested dose was 3mg/kg. Treatment-emergent AEs were reported in 16/24 (67%) of all lanadelumab-treated subjects and in 6/8 (75%) of all placebo-treated subjects. Treatment-emergent AEs assessed by the investigator as related to investigational product were observed in 6/24 (25%) of all lanadelumab-treated subjects and in 4/8 (50%) of all placebo-treated subjects.

The most frequent treatment-related TEAE was headache, reported by five of lanadelumab-treated subjects and one of placebo-treated subjects. All reports of headaches were mild to moderate in severity and all events resolved.

Two subjects reported severe treatment-related TEAEs of creatine phosphokinase (CPK) elevations; 1 subject in the 0.1 mg/kg group and 1 subject in the placebo group. Neither treatment-related, severe elevation of CPK was associated with any other adverse event or finding that might indicate clinical importance, such as myalgia or muscle weakness. In both subjects, the CPK elevations were absent or reduced at subsequent time points and appeared to be a sporadic event.

Study DX-2930-02, 2 doses (30, 100, 300 or 400 mg), 14 days apart

Treatment-emergent AEs were reported in 14/24 (58%) of all lanadelumab-treated subjects and in 10/13 (77%) of all placebo-treated subjects. Treatment-emergent AEs assessed by the investigator as related to investigational product were observed in 7/24 (29%) of lanadelumab-treated subjects and in 5/13 (39%) of placebo-treated subjects.

The most frequent TEAEs considered treatment-related in lanadelumab-treated subjects were injection site pain (25%), followed by headache (8%), and injection site erythema (4%). Other TEAEs considered treatment-related included vomiting, injection site edema, and night sweats, each reported in one lanadelumab-treated subject, and hereditary angioedema and abdominal discomfort, each reported in one placebo-treated subject.

Severe TEAEs occurred in 6/24 (25%) of lanadelumab-treated subjects and in 5/13 (39%) of placebo-treated subjects. The most common severe TEAE was hereditary angioedema, experienced by 3 (12.5%) lanadelumab -treated subjects and 5 (38.5%) placebo-treated subjects. 2/24 lanadelumab-treated subjects had severe TEAEs considered treatment-related (severe injection site pain in one patient and worsening headache and nightsweats in one patient). 0/13 placebo-treated subjects had severe TEAEs considered treatment-related. One placebo-treated subject experienced an SAE (pneumonia).

2.6.1. Discussion on clinical safety

The demographic profile of subjects included in the phase 3 trials is generally considered representative for HAE patients, although it is noted that overweight and obese patients might be overrepresented. It is acknowledged that there was a baseline imbalance in weight and BMI in study DX-2930-03, with a higher proportion of heavy subjects in the lanadelumab group. It is also noted that the ethnicity of the safety population is almost exclusively white. No firm conclusions can be drawn from the relatively few patients in the adolescent (n=23, 10%) or elderly population (>65 years) (n=10, 4.5%). On the other hand, current findings do not suggest an increased risk.

Overall in the placebo controlled study DX-2930-03, there were more TEAEs in the lanadelumab treated group compared to placebo, 91% vs 76%, more related TEAEs 60% vs 34% and more serious TEAEs 5% vs 0%. Numerically there is a trend that the highest dose group, 300 mg q2 wks, had more TEAEs and more related TEAEs compared to the other lanadelumab groups.

No deaths and no related serious TEAEs were reported during the studies.

Among the most common adverse events reported were viral respiratory upper tract infections; these adverse events were equally common in both groups. Headache was also commonly reported in both groups.

In study DX-2930-03, related TEAEs are dominated by injection site reactions in the lanadelumab group, injection site pain 42% injection site erythema 9.5%, injection site bruising, 6%. ISR were also common in the ongoing open-label study (DX-2930-04). In the pooled phase 3 lanadelumab treated population (n=220), 15 SAEs were reported in 11 subjects. There are small numbers in each group and no specific pattern can be found. It is noted that none of the SAEs was considered related to the study treatment.

Since lanadelumab is intended for long-term use, it is of interest to know if the frequency of AEs changes over time. No placebo-controlled data is available after 6 months of treatment but open label extension study is ongoing. An updated summary of the safety profile of lanadelumab based on the 120 days safety update data cut on 01 Jan 2018 (4 months of additional information available from the ongoing Study DX-2930-04 since the initial filing) is provided and supports the safety conclusions drawn from the data in the original submission. More specifically, a comparison of study DX-2930-03 and DX-2930-04 regarding incidence rates for the pooled lanadelumab treated population suggests that the incidence rates for TEAEs are not increasing over time. Moreover, no treatment-related SAEs or deaths were reported and no additional related severe TEAEs have been reported since the initial submission. There was no increase in SAEs or AESIs with longer term exposure to lanadelumab.

Common adverse events in the overall lanadelumab treated group are consistently overlapping between study DX-2930-03 and study DX-2930-04, with the exception of injection site pain, which tend to occur more often in the placebo controlled study. The rates of discontinuations are 6/84 in study DX-2930-03 compared to 7/76 in study DX-2930-04. AE reported as a reason for discontinuation concerns one patient in each study.

Altogether, data do not suggest that common adverse events or discontinuations would increase over time (and therefore be more common in the follow-up study).

Hypersensitivity reactions are recorded in the lanadelumab treated population, n=5 in the pivotal study. In study DX-2930-04, hypersensitivity reactions accounts for three out of five discontinuations due to adverse events. It is noted that there are so far no anaphylactic reactions reported in the study population.

Lanadelumab is a monoclonal antibody. Interactions with other drugs are not anticipated due to the nature and metabolism of lanadelumab. The overall prevalence of ADAs is under 12% in lanadelumab treated subjects. Pre-existing ADA positivity is 1.4%. There is no hypersensitivity safety findings related to ADA positivity.

There is a mechanistic plausibility for lanadelumab to increase aPTT. In study DX-2930-03, aPTT was balanced between groups at baseline and increases during the study are in line with what can be predicted from primary pharmacology. The increase in aPTT seems dose-dependent and changes appear from the first measurement after study start, i.e. day 28. These changes are then maintained throughout the study period up to day 182. Changes are largest in the 300 mg q2wks group and they are in the range of 6–8 sec from baseline value of 28 sec (<29% increase). Increases in aPTT are according to the applicant small and 83/84 lanadelumab treated subjects had aPTT <1.5 x ULN. In DX-2930-04 aPTT was monitored and the change from baseline was increased to a similar extent, at most 5.71 seconds at day 224 on group level. For the individual subject with the largest increase, aPTT was increased 86.9 s. The actual value was 120.5 s at day 56 during the dose and wait period and confounded by concomitant heparin use.

No bleeding events were observed in association with a prolonged aPTT, and no effects on PT, INR were observed in subjects treated with lanadelumab. It is therefore concluded that increases in aPTT are not considered related to an increased risk of bleeding and that the observed aPTT prolongations are therefore not clinically relevant. Overall, presented findings are supportive of the view that increased aPTT levels can be considered as laboratory finding consistent with the mechanism of action.

In the placebo controlled study DX-2930-03 four lanadelumab treated subjects and zero placebo treated subjects had elevated ALAT >3X ULN during the study. One patient discontinued lanadelumab treatment due to elevated transaminases and the transaminases fell after treatment discontinuation, which could be interpreted as a positive dechallenge. In the three patients with elevated ALAT >3X ULN who continued study DX-2930-03, ASAT/ALAT elevations were asymptomatic and not considered clinically significant. It is concurred that 2/4 patients had pre-existing liver disease (hepatic steatosis). However, ALAT levels are markedly higher at baseline in the lanadelumab 300 mg every 2 weeks treated group and also higher in the overall lanadelumab treated groups. ALAT levels do not increase in lanadelumab treated groups during the 6-month study period. Based on the presented findings it is considered appropriate to include ASAT/ALAT elevations as possible adverse reactions to lanadelumab treatment. There is insufficient evidence to suggest that individuals with chronic liver disease and cirrhosis are at increased risk of drug induced liver injury while on lanadelumab. Patients with AT elevations can thus be given lanadelumab.

In PK analyses, weight was shown to be a significant covariate for lanadelumab, i.e. low-weight patients are predicted to have a higher exposure than the average 70 kg patient. In total, seven subjects <50 kg were treated with lanadelumab in the two phase 3 studies; one in DX-2930-03 and seven in DX-2930-04 (the subject in DX-2930-03 was treated also in DX-2930-04).
In study DX-2930-03, two TEAEs were reported by the single lanadelumab treated subject and non by the two placebo treated subjects. None of the TEAEs was considered related to treatment and none was serious or severe.
In study DX-2930-04, the rate of related TEAEs/ subject year was higher in the <50 kg subgroup compared to other subgroups. It is however noted that in the <50 kg subgroup, 3/7 subjects reported 67 related TEAEs, i.e. 93% of all reported TEAEs in this subgroup. No AESI or serious or severe AE were reported in subjects <50 kg. In study DX-2930-04, 68/72 (94.4%) of all TEAE and 67/67 (100%) of all related TEAEs in the <50 kg subgroup were injection site reactions. One event of drug hypersensitivity was reported, but was not deemed as related. Current findings do not suggest any specific safety issues in this population. Injections site reactions are not presumed to be secondary to a high systemic exposure, however a lower lanadelumab dose in subjects <50 kg is introduced in the SmPC due to the higher exposure in these patients.

2.6.2. Conclusions on clinical safety

Safety concerns for lanadelumab include mainly injection site reaction (transient, mostly of mild intensity). However, there were also episodes of hypersensitivity (some local, other more systemic), which could be expected for a monoclonal antibody. There is a mechanistic plausibility for lanadelumab to increase aPTT. The increase in aPTT seems dose-dependent do not seem to increase after the first month. No bleeding events were observed in association with a prolonged aPTT, and no effects on PT, INR were observed in subjects treated with lanadelumab. It is therefore concluded that increases in aPTT are not considered related to an increased risk of bleeding and that the observed aPTT prolongations are therefore not clinically relevant.

Liver enzyme elevations were observed in the phase 3 studies and patients with elevated transaminases were excluded at study start. In the pivotal study, however, no changes were observed at the group level. It is nevertheless agreed that liver toxicity is included as an important potential risk in the RMP.

Long term safety data remain limited and will be provided in the post authorisation setting.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Hypersensitivity
Important potential risks	• Immunogenicity • Liver Toxicity
Missing information	• Long-term safety in paediatric population • Long-term safety in adult population • Use in Pregnancy and Lactation

Pharmacovigilance plan

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due Date(s)
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
N/A	N/A	N/A	N/A	N/A
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				
N/A	N/A	N/A	N/A	N/A
Category 3 – Required additional pharmacovigilance activities				
HELP Study Extension ™ DX-2930-04 ONGOING	**Primary Objective:** • To evaluate the long-term safety of repeated SC administrations of DX-2930 **Secondary Objectives:** • To evaluate the long-term efficacy of DX-2930 in preventing HAE attacks • To characterize the outer bounds of dosing frequency for DX-2930 **Tertiary Objectives:** • To assess the immunogenicity of	• Long-term safety in paediatric population • Long-term safety in adult population • Hypersensitivity • Immunogenicity • Liver Toxicity • Use in Pregnancy and lactation	FSI	26 May 2016
			Interim Report	23 Nov 2017
			LSO	Nov 2019
			Final CSR	May 2020

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due Date(s)
	chronically administered DX-2930 • To evaluate the effect of DX-2930 on health-related QoL • To characterize the PK and PD profiles of SC administration of DX-2930 • To evaluate safety and efficacy in the non-rollover population of switching from LTP treatment to DX-2930 • To assess the clinical response of rescue medications for the treatment of acute angioedema attacks while on DX-2930 therapy (applicable for subjects ≥18 years of age)			

CSR = Clinical Study Report, FSI = First Subject In, LSO = Last Subject Out, Ministry of Health, Labor and Welfare = MHLW, Long-term prophylactic = LTP, pharmacokinetic = PK, pharmacodynamic = PD, Pharmaceuticals and Medical Devices Agency = PMDA, quality of life = QoL, subcutaneous = SC

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hypersensitivity	Routine risk minimisation measures: • SmPC sections 4.8 • SmPC sections 4.4 state management of hypersensitivity • Package Leaflet sections 2 and 4 explain how to detect early signs and symptoms of hypersensitivity and report in Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • HELP Study Extension ™ (DX-2930-04)
Immunogenicity	Routine risk minimisation measures: • SmPC section 4.8 describe immunogenicity	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • None	• None Additional pharmacovigilance activities: • HELP Study Extension ™ (DX-2930-04)
Liver Toxicity	Routine risk minimisation measures: • SmPC section 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Long-term safety in paediatric population	Routine risk minimisation measures: • SmPC Label and Package Leaflet caution with use in children as there is limited information Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • HELP Study Extension ™ (DX-2930-04)
Long-term safety in adult population	Routine risk minimisation measures: • No risk minimisation activities are proposed. Additional information will be available after completion of HELP Study Extension ™ (DX-2930-04). Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • HELP Study Extension ™ (DX-2930-04)
Use in Pregnancy and Lactation	Routine risk minimisation measures: • SmPC section 4.6 describe Pregnancy, Fertility and Lactation Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • HELP Study Extension ™ (DX-2930-04)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 23 August 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that lanadelumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers lanadelumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, TAKHZYRO (lanadelumab) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HAE is a rare autosomal dominant disorder caused by mutations in the gene coding for C1 esterase inhibitor (C1-INH). Deficiency of C1-INH is believed to result in the loss of inhibition of plasma kallikrein activity leading to increased bradykinin release.
HAE is characterized by unpredictable recurrent episodes of debilitating subcutaneous or submucosal oedema typically affecting the skin, upper airway, and gastrointestinal tract. The attacks are often painful. The condition has a large negative impact on both daily life and quality of life for the patients. Moreover, approximately 50% of all patients with HAE will experience a potentially life-threatening laryngeal attack in their lifetime (Bork et al., 2006).

Lanadelumab is a recombinant fully human IgG1 monoclonal antibody inhibitor of active plasma kallikrein. The aim of the treatment is to prevent HAE attacks by inhibiting plasma kallikrein, thereby preventing the release of bradykinin from HMWK (high molecular weight kininogen). Lanadelumab is not intended for acute treatment of HAE attacks.

Lanadelumab is administered subcutaneously. Orphan designation has been granted for lanadelumab in the treatment of HAE.

3.1.2. Available therapies and unmet medical need

For prevention of HAE attacks, current treatment guidelines recommend C1-INH replacement therapy or attenuated androgens as standard of care. Tranexamic acid may also be tried.
For the time being, Cinryze (plasma derived C1-INH concentrate) is the only centrally approved medicinal product in the EU. Cinryze is administered intravenously every 3-5 days. This is cumbersome for the patient and also for the health care, as intravenous injections/infusions are generally not administered as self-treatment.

While existing preventive therapy with C1-INH ameliorates the number and severity of attacks, some patients still experience breakthrough attacks, which may be life-threatening as described above. There is therefore a medical need for alternative therapies. Lanadelumab provides an alternative for patient care that is administered via SC injection with a dose regimen of administration every 2 weeks.

3.1.3. Main clinical studies

Study DX-2930-03 was a Phase 3, multicentre, randomized, double-blind, placebo-controlled HAE prevention study with 26 weeks treatment duration in subjects ≥ 12 years with HAE type I or type II and with a baseline HAE-attack rate of at least 1 per 4 weeks during the run-in period. The total number of participants was 125 (placebo 41; lanadelumab 84). Three lanadelumab dosing regimens were compared (150 mg q4wks, 300 mg q4wks and 300 mg q2wks). The primary objective was to evaluate the efficacy of lanadelumab in preventing HAE attacks.

The ongoing open-label extension study DX-2930-04 enrolled 212 subjects; 109 “rollovers” from study DX-2930-03 and 103 “non-rollovers” (whereof 19 subjects from study DX-2930-02). All subjects received lanadelumab 300 mg q2wks. Interim analyses from the extension study are provided as supporting data in the MAA.

The clinical development program consisted also of a “proof-of-concept”, randomized, double-blind, placebo-controlled, multiple ascending dose-finding study DX-2930-02 enrolling in total 37 subjects (13 placebo, 24 lanadelumab). The lanadelumab doses used were 30 mg, 100 mg, 300 mg and 400 mg.

3.2. Favourable effects

The DX-2930-03 pivotal study met the primary and the three secondary efficacy endpoints for all lanadelumab treatment arms.

The primary efficacy endpoint was the number of investigator confirmed HAE attacks during the treatment period (Day 0 through Day 182).

Poisson regression of investigator-confirmed HAE attacks during the treatment period (D 0 to D 182) by treatment group- (ITT Population) shows reductions in the least squares mean HAE attack rate (reduction range: 73 % to 87 %; adjusted p<0.001) in all lanadelumab treatment arms compared to placebo: -75.6 (-84.6, -61.2) in the 150 mg q4wks arm, -73.3 (-82.4, -59.5) in the 300 mg q4wks arm, and -86.9 (-92.8, -76.2) in the 300 mg q2wks arm.
The least squares mean HAE attack rate (95% CI of rate [attacks/4 weeks]) was 0.48 (95% CI: 0.31, 0.74) in the 150 mg q4wks arm, 0.53 (0.36, 0.77) in the 300 mg q4wks arm, and 0.26 (0.14, 0.46) in the 300 mg q2wks arm, compared to 1.97 (1.64, 2.36) in the placebo arm. This corresponds to a reduction in the least squares mean investigator-confirmed HAE attack rate compared to placebo of 75.6%, 73.3%, and 86.9% respectively (adjusted p<0.001).

The secondary efficacy endpoints were :

- the number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period (Day 0 through Day 182).
The estimated least squares mean HAE attack rate (95% CI: range) was 0.31 (95% CI: 0.18, 0.54) in the 150 mg q4wks arm, 0.42 (95% CI: 0.28, 0.65) in the 300 mg q4wks arm, and 0.21 (95% CI: 0.11, 0.40) in the 300 mg q2wks arm, compared to 1.64 (95% CI: 1.34, 2.00) in the placebo arm.

- the number of moderate or severe investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182).
The least squares mean HAE attack rate (95% CI, range) was 0.36 (0.22, 0.58) in 150 mg q4wks arm, 0.32 (95% CI: 0.20, 0.53) in 300 mg q4wks arm, 0.20 (95% CI: 0.11, 0.39) in 300 mg q2wks arm relative to 1.22 (95% CI: 0.97, 1.52) in the placebo arm.

- the number of investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182.
The least squares mean HAE attack rate (95% CI: range) was 0.44 (95% CI: 0.28, 0.70) in the 150 mg q4wks arm, 0.49 (95% CI: 0.33, 0.73) in the 300 mg q4wks arm, 0.22 (95% CI: 0.12, 0.41) in the 300 mg q2wks arm, relative to 1.99 (95% CI: 1.65, 2.39) in the placebo arm.

Furthermore, the preliminary results of study DX-2930-04 indicate that for subjects previously treated with lanadelumab in study DX-2930-03, the lanadelumab effect on HAE attack rate is maintained.

Subjects <18 years

8.0% of the subjects in the pivotal study were adolescents aged ≥12 to <18 years; however, the absolute number of subjects was low (N = 10; placebo 4, lanadelumab 6). In the extension study DX-2930-04, 21

subjects ≥12 to <18 years (9.9% of study population) were treated with lanadelumab, including 8 rollovers from DX-2930-03. In total, 23 unique subjects <18 years were treated with lanadelumab in the phase 3 studies.

In study DX-2930-03, the reduction in mean HAE attack rate was numerically larger in the lanadelumab treatment arms (0.30 [SD=0.26] and 0.31 [0.433] for 300 mg q4wks and 300 mg q2wks, respectively) compared to placebo (0.92 [0.99]); however, possibly due to low number of subjects, the difference was not statistically significant.

In study DX-2930-04, the mean HAE attack rate was 0.18 attacks/months in subjects <18 years compared to 0.30 attacks/month in the entire population (rollovers and non-rollovers); however, the baseline attack rate was also lower among adolescents than in the entire population (1.6 vs 3.0 attacks/month).

3.3. Uncertainties and limitations about favourable effects

In all clinical studies, only subjects with HAE type I or II were included. Those conditions are characterised by either a deficiency or a dysfunction of C1-esterase inhibitor (C1-INH), leading to dysregulation of plasma kallikrein activity. “HAE with normal C1-INH activity”, i.e. HAE other than HAE1 or HAE2, is a heterogeneous entity comprising of e.g. HAE caused by mutations in the coagulation factor XII (F12) gene, the plasminogen (PLG) gene, or the angiopoietin-1 gene (ANGPT1). In many cases the aetiology is unknown.
The Applicant has presented supporting data from the literature that subjects with F12-HAE and PLG-HAE, may have an increased FXII activation, implicating a role for the kallikrein-kinin system in angioedema formation also in this population.”

The CHMP agreed to recommend the 300 mg q2wks dosage as starting dose, based on the magnitude of the effect, which is numerically larger than that of the other two dosing regimens, although the treatment arms were not formerly compared with one another. Furthermore, PK/PD considerations seem to favor q2w administration (e.g. exposure-response analysis, achievement of steady state concentrations).

In total, only 23 unique subjects <18 years were exposed to lanadelumab in the development program. In the population pharmacokinetic modelling, an approximately 37% higher exposure in adolescents than adults was predicted. However, the AUC range was quite large; 121- 832 ug*d/ml in adults and 321-1050 ug*d/ml in adolescents. The difference in exposure is presumed to be secondary to the differences in mean weight between the populations. Given the broad ranges of exposure in both adults and adolescents, it is considered that the increased exposure in adolescents would not exert any major impact on efficacy and safety.

Pharmacokinetic analyses suggest a lower exposure in subjects with higher body weight, raising the possibility that the proposed dosing regimen would not be effective in heavy subjects. However data from ad-hoc subgroup analysis based on weight showed that 300 mg Q2W showed a favourable effect on HAE attack rates. This was confirmed in the DX 2930-04 study. Using PK/PD data, the 300 mg q2wks dosing was associated with lanadelumab exposure approximate or above the IC90 of PD and EAUC90 for efficacy in patients across a large range of body weight (46.8-150 kg). This is adequately addressed in the posology section of the SmPC.

3.4. Unfavourable effects

Safety data are generated from the placebo-controlled pivotal 6-month study DX-2930-03, which included 125 subjects (84 active, 41 placebo). The open-label study DX-2930-04 contributes with long-time data (up to 12 months) in 75 subjects. Overall in the pivotal study, there were more TEAEs in the lanadelumab treated group compared to placebo, 91% vs 76%, more related TEAEs 60% vs 34% and more serious TEAEs 5% vs 0%.

Numerically there is a trend that the highest dose group, 300 mg q2 wks, had more TEAEs and more related TEAEs compared to the other lanadelumab groups. Related TEAEs are dominated by injection site reactions in the lanadelumab group; injection site pain 42%, injection site erythema 9.5%, injection site bruising 6%. Overall pooled data for DX-2930-03 and DX 2930-04 (n=220) shows that Injection Site Reactions were the most frequently reported TEAEs (53% of lanadelumab-treated population).

Hypersensitivity reactions are recorded in the lanadelumab treated population, n=5 in the pivotal study and its extension. In study DX-2930-04, hypersensitivity reactions accounts for 3/5 discontinuations due to adverse events.

There was a dose-dependent increase in aPTT and changes appear from the first measurement after study start, i.e. day 28. These changes were maintained throughout the study period up to day 182. Changes in the 300 mg q2wks group were in the range of 6–8 sec from baseline value of 28 sec (<29% increase). 83/84 lanadelumab treated subjects had aPTT <1.5 x ULN. In DX-2930-04 aPTT was monitored and the change from baseline was increased to a similar extent, at most 5.71 seconds at day 224 on group level. No bleeding events were observed in association with a prolonged aPTT, and no effects on PT, INR were observed in subjects treated with lanadelumab.

Pooled phase 3 safety data shows that elevated ALAT >3X ULN (regardless of baseline - with up to 3X allowed) was reported in 10 subjects. Subjects with elevations were asymptomatic, with no associated hyperbilirubinemia (no Hy's Law cases) or elevated alkaline phosphatase and 5/10 returned to baseline while lanadelumab was continued. No antidrug antibody formation was recorded for the 10 subjects. It is considered unknown whether lanadelumab could potentially be linked with more pronounced liver toxicity in a larger treatment population. Therefore this is a safety concern and included in the RMP as an important potential risk.

3.5. Uncertainties and limitations about unfavourable effects

Since lanadelumab is intended for long-term use, it is of interest to know if the frequency of AEs changes over time. No placebo-controlled data is available after 6 months of treatment but open label extension study is ongoing. A comparison of study DX-2930-03 and DX-2930-04 regarding incidence rates for the pooled lanadelumab treated population suggests that the incidence rates for TEAEs are not increasing over time. However the long term safety data remain limited at present and the safety profile will be monitored in the post marketing setting as stated in the RMP.

No firm conclusions can be drawn from the relatively few patients in the adolescent n=23 (10%) or elderly population (>65 years) n=10 (4.5%). On the other hand, current findings do not suggest an increased risk. Lanadelumab is not intended for acute treatment of HAE attacks. Therefore, during the study rescue medication were allowed in the event of an HAE attack. Drug interactions associated with use of such HAE co-medications have not been evaluated. Lanadelumab is a monoclonal antibody and pharmacokinetic interactions with other drugs are not anticipated but pharmacodynamics interactions could theoretically be a concern. This will be addressed in the post authorisation setting.

In PK analyses, weight was shown to be a significant covariate for lanadelumab, i.e. low-weight patients are predicted to have a higher exposure than the average 70 kg patient. In total, 7 subjects <50 kg were treated with lanadelumab in the two phase 3 studies. In study DX-2930-04, the rate of related TEAEs/ subject year was higher in the <50 kg subgroup compared to other subgroups. (representing 93% of all reported TEAEs). All related TEAEs in the <50 kg subgroup were injection site reactions. Current findings do not suggest any specific safety issues in this population. Injections site reactions are not presumed to be secondary to a high systemic exposure, therefore a lower lanadelumab dose in subjects <50 kg is not considered necessary. However in

patients who are attack free for long period a reduction of frequency of administration may be considered especially in low weight patients.

3.6. Effects Table

Table 35 Lanadelumab

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
HAE-attacks	Lanadelumab 150 mg q4wks vs placebo	(attack/4 wks)	0.48 (0.31,0.74)	1.97 (1.64,2.36)	P<0.001	DX-2930-03
	Lanadelumab 300 mg q4wks vs placebo	(attack/4 wks)	0.53 (0.36,0.77)	1.97 (1.64,2.36)	P<0.001	
	Lanadelumab 300 mg q2wks vs placebo	(attack/4 wks)	0.26 (0.14,0.46)	1.97 (1.64,2.36)	P<0.001	
HAE-attacks requiring Acute treatment	Lanadelumab 300 mg q2wks vs placebo	(attack/4 wks)	0.21 (0.11,0.40)	1.64 (1.34,2.00)	P<0.001	DX-2930-03
Moderate /severe HAE attacks	Lanadelumab 300 mg q2wks vs placebo	(attack/4 wks)	0.20 (0.11,0.39)	1.22 (0.97,1.52)	P<0.001	DX-2930-03
Unfavourable Effects						
Any TEAE	Pooled lanadelumab groups vs placebo	N (%)	76/84 (91%)	31/41 (76%)		Study DX-2930-03
Injection site pain Injection site erythema Injection site bruising	Pooled lanadelumab groups vs placebo	N (%)	36/84 (43%) 8/84 (9.5%) 6/84 (7.1%)	12/41 (29%) 1/41 (2.4%) 0/41 (0%)		Study DX-2930-03
aPTT change from baseline, day 182	Pooled lanadelumab groups vs placebo	Sec. +/- SD	4.7 +/-5.0	-1.2 +/-4.3		Study DX-2930-03
ALAT/ASAT elevations, >3 x ULN	Pooled lanadelumab groups vs placebo	N	4	0		Study DX-2930-03

Abbreviations: HAE hereditary angioedema; wks weeks; q2wks (q3wks) every 2 (4) week; TEE treatment emergent adverse event; aPTT activated partial thromboplastin time; ALAT alanine aminotransferase; ASAT aspartate aminotransferase; ULN upper limit of normal

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

As HAE attacks are unpredictable, associated with considerable discomfort for the patient and potentially lethal, prevention of such attacks is considered to be of high clinical relevance. Lanadelumab has a different mode of action from alternative existing treatments. In international guidelines, C1-INH replacement therapy is recommended as first line treatment. In the EU, the only centrally approved C1-INH replacement therapy, Cinryze, is administered intravenously every 3-5 days. In comparison, lanadelumab which is administered subcutaneously every 2-4 weeks offers a significant advantage even considering the recently approved product (Berinert) since subcutaneous injections are administered more frequently. The efficacy endpoints reflect not only the total HAE attack rate and severity during the treatment period, but also other measures of HAE attack prevention, e.g. time to first HAE attack and quality of life. Consistent through the efficacy analyses, all lanadelumab treatment arms were superior to placebo.

In an ad hoc analysis with pooled data from all three lanadelumab treatment arms compared to placebo, the result of all subgroups (e.g. age, weight, baseline HAE attack rate) were consistent with those of the entire population.

Pharmacokinetic analyses suggest a lower exposure in subjects with higher body weight as well as a higher exposure in subjects with low weight. Based on the safety data for subjects <50 kg and the relatively benign safety profile of lanadelumab in general and on the predicted effect of lanadelumab up to 150 kg, the benefit/risk ratio for a flat dose (300 mg q2w) is considered positive.

Lanadelumab is injected subcutaneously and injection site reactions are the most common related adverse events. So far there are no anaphylactic reactions reported, although such reactions could be expected to occur in a larger population. Lanadelumab is intended for long-term treatment of HAE and the data base is relatively small, only approximately 100 patients treated for more than one year. Therefore the overall amount of long term safety data is still sparse and will be collected through the post marketing setting in the ongoing DX-2930-04 study.

Overall, the safety profile is considered to be favourable considering the clinical benefits shown. However, enzyme elevations do occur during lanadelumab treatment and it such transaminase elevations could currently be regarded as idiosyncratic. It is still considered unknown whether lanadelumab could potentially be linked with more pronounced liver toxicity in a larger treatment population. This is addressed in the SmPC section 4.8 in and RMP as liver toxicity is considered an important potential risk.

3.7.2. Balance of benefits and risks

The benefit of the product has been adequately shown for prevention of HAE attacks i.e. a condition with high mortality in spite of existing available products . The assessment of the safety profile is based on limited data but is considered acceptable. Identified and potential safety issues are considered to be clearly outweighed by convincing efficacy data.

The indication *"[Lanadelumab] is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older"* is considered justified.

The wording “routine prevention” indicates that lanadelumab is intended for continuous treatment as opposed to e.g. short term prevention at surgery. This is an established wording within this therapeutic field.

In all clinical studies, only subjects with HAE type I or II were included. However, literature support that the kallikrein-kinin system is also involved in angioedema formation in HAE of other types than HAE type I or II, supporting a broad HAE indication. Therefore extrapolation to other subtypes is acceptable by CHMP. Additionally, it is clearly stated in section 4.4 and 5.1 of the SmPC that only subjects with HAE type I and II were included in the studies.

Data in adolescents is still limited but indicates similar efficacy and safety profile than in adults.

A history of recurrent attacks was a prerequisite for inclusion in all three studies. The treatment period attack rate was strongly influenced by the baseline attack rate, however, in all subgroups, the decrease in HAE attack rate was larger in the lanadelumab treatment arms compared to placebo. However, the benefit/risk ratio for subjects having had only one single attack cannot be considered positive. This is reflected in section 4.1 of the SmPC.

HAE is a genetic disease and would be an interesting treatment option also in younger children. Currently the <12 years old population has not been studied, although the applicant is planning for a paediatric study which addresses this important medical need.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of TAKHZYRO is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that TAKHZYRO is not similar to Firazyr within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of TAKHZYRO is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that lanadelumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union