14 September 2023
EMA/440820/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Takhzyro

International non-proprietary name: Lanadelumab

Procedure No. EMEA/H/C/004806/X/0034/G

Note

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

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Table of contents

List of abbreviations

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
C1-INH	C1 esterase inhibitor
Cavg,ss	average concentration at steady-state
Cmax,ss	maximum concentration at steady-state
Cmin,ss	minimum concentration at steady-state
cHMWK	cleaved high molecular weight kininogen
CHO	chinese hamster ovary
CPP	critical process parameter
CQA	critical quality attribute
CSR	clinical study report
CV	coefficient of variation
DS	drug substance
EC	European Commission
EMA	European Medicines Agency
EP	European pharmacopoeia
EOS	end of study
EU	European Union
GMP	Good manufacturing practice
HAE	hereditary angioedema
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
ISO	International standard organisation
ISR	injection site reaction
LTP	long-term prophylaxis
MedDRA	Medical Dictionary for Regulatory Activities
NOR	normal operating range
OLE	open-label extension
PAR	proven acceptable range

PD	pharmacodynamics
PFS	pre-filled syringe
Ph Eur	European pharmacopoeia
PK	pharmacokinetics
pKal	plasma kallikrein
PPQ	process performance qualification
PT	preferred term
q2wks	every 2 weeks
q4wks	every 4 weeks
SC	subcutaneous
SD	standard deviation
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
VAS	visual analogue scale

1. Background information on the procedure

1.1. Submission of the dossier

Takeda Pharmaceuticals International AG Ireland Branch submitted on 9 November 2022 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	IB

Extension application to add a new strength of 150 mg for lanadelumab solution for injection in pre-filled syringe and to extend the indication to include paediatric use (2 to <12 years).
The new indication is only applicable to the new 150 mg strength presentations.

The RMP (version 3.0) is submitted in accordance.

In addition, a type IB variation (C.I.z) has been submitted to update section 7 of the Package Leaflet (PL) for the 300 mg in 2 ml pre-filled syringe (EU/1/18/1340/004-006) in line with the proposed PL for the 150 mg in 1 ml pre-filled syringe (new strength).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations.

TAKHZYRO, was designated as an orphan medicinal product EU/3/15/1551 on 09 October 2015 in the following condition: the treatment of hereditary angioedema.

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0214/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0214/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0214/2022.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan

medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

The application was received by the EMA on	9 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 February 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 February 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 March 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	12 May 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 June 2023
The PRAC Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	29 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	6 July 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	20 July 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	11 August 2023
The PRAC Rapporteur circulated the Assessment Report on the responses to the list of outstanding issues to all CHMP and PRAC members on	17 August 2023

The CHMP Rapporteur circulated the Assessment Report on the responses to the list of outstanding issues to all CHMP and PRAC members on	30 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP Rapporteur circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 September 2023
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	14 September 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The currently approved indication is TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.

The proposed new indication is TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged **2** years and older.

2.1.2. 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.

The estimated prevalence of HAE in the general population is one individual per 50,000, with reported ranges from 1:10,000 to 1:150,000 (Ghazi A, Grant JA. Biologics. 2013;7:103-13).

2.1.3. Aetiology and pathogenesis

Hereditary angioedema is caused by mutations in the *SERPING1* 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 (pKal) 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.

2.1.4. 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).

The reported median age of first symptom onset varies in the literature, but symptoms often begin in childhood or adolescence (Maurer et al. 2018) with angioedema episodes usually beginning between 5 and 11 years of age (Farkas 2010). Per the WAO/EAACI guidelines revised in 2017, the median age of symptom onset is approximately 12 years of age. The mean age for first symptom onset reported from large studies is 6 to 12 years of age (Bork et al, 2006; Bygum et al, 2011; Farkas 2010; Roche et al, 2005). Limited information on cases of HAE attacks is available in the literature on children younger than 3 years of age (Bygum et al, 2011; El-Hachem et al, 2005; Nanda et al, 2015; Roche et al, 2005. While the prevalence of patients who have HAE attacks is low in the paediatric population <6 years, abdominal and cutaneous attacks have been reported in children as young as 1 year of age (Agostini et al, 2004; Bork et al, 2006), and laryngeal attacks have been reported in children as young as 3 years of age (Craig et al, 2012; Farkas 2010).

The diagnosis of hereditary angioedema is made by clinical evaluation, patient history, and blood tests that detect decreased levels of complement proteins. In instances of high clinical suspicion and recurrent episodic angioedema of uncertain aetiology, genetic testing is indicated.

2.1.5. Management

Current available treatment options for subjects aged 2 to <12 years are summarised in Table 1.

Table 1: Current Therapeutic Options for Hereditary Angioedema Patients 2 to <12 Years of Age

Approved Therapy	Type of Treatment	Route of Administration	Age	Region
FIRAZYR®	On-demand/acute therapy	SC	≥2 years	EU[a]
HAEGARDA®	Prophylaxis	SC	≥6 years	US
BERINERT®	On-demand/acute therapy; PPP	IV	Pivotal study ≥10 years; PK and safety ≥5 years	US[b] and EU
	Prophylaxis	IV	≥6 years	EU
CINRYZE®	On-demand/acute therapy; PPP	IV	≥2 years	EU
	Prophylaxis	IV	≥6 years	US and EU
RUCONEST®	On-demand/acute therapy	IV	≥2 years	US[c] and EU

EU=European Union; IV=intravenous; PPP=pre-procedure prevention; SC=subcutaneous; US=United States
a Approved in patients >18 years in the US
b Only approved for on-demand use in the US
c Approved in patients ≥13 years in the US

In the EU, only Cinryze, Orladeyo and Takhzyro are currently approved for routine prevention of HAE attacks; Cinryze in subjects ≥6 years, and Takhzyro and Orladeyo in subjects ≥12 years. Cinryze is administered intravenously every 3-4 day. Intravenously administered Berinert is indicated for pre-procedure prevention only and not for routine prophylaxis in the paediatric population, whereas subcutaneously administered Berinert is authorised for prevention of recurrent hereditary angioedema attacks in adolescents and adults. Furthermore, antifibrinolytic agents (mainly tranexamic acids) are indicated as HAE prophylaxis. In clinical practice, tranexamic acid seems to be mainly used in subjects in which C1-INH replacement therapy is not available or not approved, e.g., children and pregnant women.

2.2. About the product

Lanadelumab is a recombinant, fully human immunoglobulin G (IgG) 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.

2.3. Type of application and aspects on development

Lanadelumab was first approved under the trade name of Takhzyro for routine prophylaxis to prevent attacks of hereditary angioedema in patients 12 years and older in the United States (23 Aug 2018), Canada (19 Sep 2018), and European Union (22 Nov 2018). Currently, lanadelumab is approved in over 50 countries globally.

The initial approval was based on results from 4 registrational trials: 2 Phase 1 studies (Study DX-2930-01 and Study DX-2930-02); 1 pivotal Phase 3 study (Study DX-2930-03 [HELP Study]); and 1 Phase 3 open label extension (OLE) study (Study DX-2930-04 [HELP Study Extension]).

Study SHP643-301 is part of the PIP ("Study 3"). According to the Compliance report (EMEA-C-001864-PIP01-15-M07; PIP decision number P/0214/2022), compliance with the PIP for this study was confirmed.

2.4. Quality aspects

2.4.1. Introduction

This is an extension application to add a new strength of 150 mg for lanadelumab solution for injection in pre-filled syringe (PFS) and to extend the indication to include paediatric use (2 to <12 years). The new indication is only applicable to the new 150 mg strength presentations.

The finished product is presented as a sterile preservative-free solution for injection for subcutaneous administration containing 150 mg of lanadelumab as active substance.

Other ingredients are: disodium phosphate dihydrate, citric acid monohydrate, histidine, sodium chloride, polysorbate 80, and water for injections.

The lanadelumab 150 mg PFS finished product formulation is identical to the formulation in the commercial finished product presentations (300 mg vial and 300 mg PFS).

The product is available in a pre-filled glass (Type I) syringe with bromobutyl stopper.

2.4.2. Active Substance

As the active substance is the same as for the 300 mg vial presentation and the 300 mg PFS presentation, no new information was submitted.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Lanadelumab finished product is a sterile preservative-free solution for subcutaneous administration of lanadelumab at a concentration of 150 mg/mL and is provided as a pre-filled syringe for a dosage strength of 150 mg.

Each pre-filled syringe is filled to deliver a nominal volume (1.0 mL) of 150 mg lanadelumab finished product. No formula overages are included.

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.

Excipients are the same as for the 300 mg vial presentation and the 300 mg PFS presentation. The excipients and their functions in the finished product are provided. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. No novel excipients or excipients of human or animal origin are used.

The finished product is manufactured by sterile filtration and aseptic filling of the active substance into syringes after thawing, pooling, mixing, and bioburden reduction filtration.

The primary container closure system consists of a 1 mL format pre-filled Type I glass syringe for 150 mg dosage, fitted with a bromobutyl rubber stopper. Each syringe is intended for single administration.

Compatibility of lanadelumab with the excipients has been demonstrated. There is no difference in the formulation between the finished product in the vial and in the PFS.

Manufacturing process development

Comparability

An overview of the changes between the 150 mg PFS and 300 mg PFS processes are described. Since there was no change in the active substance manufacturing process or the finished product formulation, the risk to product quality was expected to be minimal. To confirm the minimal impact from the process and container closure system changes on product quality for 150 mg PFS, an analytical comparability assessment was performed between lanadelumab finished product vials and 150 mg PFS. The results are highly similar and comparability can be concluded.

Container closure system

The container closure system is a pre-filled syringe consisting of a glass barrel with staked-in needle, a rubber stopper, a plunger rod and a backstopper. The container closure complies with the Ph. Eur. Requirements, as applicable. The information regarding control of the container closure parts is considered sufficient.

The 150 mg (1 mL) lanadelumab PFS for injection is a single integral product and a Notified Body opinion was provided.

The integrity of the container closure system was evaluated and considered appropriate. Based on the results from extractables and leachables studies, it is concluded that the container closure materials do pose a negligible safety risk to patients. The syringe materials are biocompatible as tested per relevant guidelines, and compatible with the finished product.

The proposed primary packaging material is considered suitable for its intended use.

Also, the ability of the secondary packaging to provide protection for lanadelumab finished product from light has been evaluated. The secondary packaging carton was shown to be effective in blocking out light and mitigating the light sensitivity. Compatibility

The biocompatibility of contacting materials was tested and all device constituent parts have been shown to be biocompatible.

2.4.3.2. Manufacture of the product and process controls

Manufacturer(s)

Lanadelumab PFS is manufactured under Current Good Manufacturing Practice (cGMP) conditions on a pre-filled syringe line in a multi-product manufacturing facility.

The 150 mg ml PFS finished product is prepared by thawing and pooling of Lanadelumab active substance, mixing, bioburden reduction and sterile filtration, aseptic filling into syringes, shipping to labeling and final assembly, secondary packaging and storage.

The manufacturing process and process controls are summarised in flow charts and tables. The purpose of each step is clearly stated, and a brief description is provided.

The lanadelumab PFS manufacturing process is controlled by process parameters (critical and non-critical) and in-process controls that have been established to ensure consistent process performance and product quality.

The control strategy for the 150 mg lanadelumab PFS manufacturing process was established in the same manner as the lanadelumab vial manufacturing process and the 300 mg PFS manufacturing process. The control strategy was developed based on current product and process understanding, which provides assurance of required process performance and final finished product quality.

A list of critical quality attributes (CQA) is provided, together with a summary of the control strategy.

It can be concluded that the descriptions of the proposed manufacturing process and process controls are acceptable. In summary, the lanadelumab 150 mg PFS finished product process is under control.

The critical process parameters (CPPs) acceptable ranges described are the proven acceptable ranges (PARs).

Process validation and/or evaluation

The 150 mg lanadelumab PFS finished product program took an integrated risk-based approach to process validation. Characterization studies were performed using small-scale models which supported the criticality assessment of CPPs and establishment of PARs and NORs. The consistency, robustness, and control of full-scale manufacturing were demonstrated through the PPQ campaign.

An extensive set of studies for process validation is presented. The process validation data provided comprise PPQ data, hold time studies, validation of aseptic processing and shipping validation.

The PPQ was successfully executed, and the study results met acceptance criteria, thus validating the commercial manufacturing process.

The process validation of the finished product manufacturing steps is adequately described and reported. Validation results for parameters, in-process controls, and attributes for the finished product are well aligned. The deviations were acceptably investigated and handled.

Procedures for aseptic processing and sterilisation are described at a sufficient level of detail. Validation data is provided and results were acceptable.

It is agreed that the process validation results support the conclusion that the manufacturing process for lanadelumab finished product can be considered validated.

2.4.3.3. Product specification

The release and shelf-life specification for lanadelumab finished product PFS has been established to ensure the identity, strength, purity, quality, and safety of the product throughout its shelf life.

The specification is consistent with the ICH Guideline Q6B. The release acceptance criteria for the finished product in syringes are the same as those for the active substance, except for the inclusion of extractable volume, attributes related to the container closure system, and device functionality.

No new product-related impurities or degradation products have been identified.

The levels of elemental impurities found (ICH Q3D) demonstrated to be acceptable to ensure the safety of lanadelumab finished product.

For the 150 mg PFS, and in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) no risk evaluation concerning the presence of nitrosamine impurities in the finished product is necessary.

Analytical procedures

The test methods used for testing lanadelumab active substance are applicable for 150 mg and 300 mg PFS.

Validation of analytical procedures

The analytical procedures used for release and stability testing of 150 mg lanadelumab finished product PFS have been qualified or validated as appropriate.

All non-compendial analytical test procedures for lanadelumab have been validated according to the ICH guideline Q2 (R1).

Batch analysis

The finished product lots were manufactured as part of process performance qualification for 150 mg PFS from the active substance lots manufactured using the commercial manufacturing process. Release test results are presented and all results met the commercial release specification for 150 mg PFS and demonstrate batch-to-batch consistency.

Reference standards or materials

As the reference standards used are the same as for the 300 mg vial and 300 mg PFS presentation, no new information has been submitted.

2.4.3.4. Stability of the product

The stability studies have been conducted in accordance with ICH guidelines. It is agreed that the proposed analytical test methods are stability indicating.

A commercial shelf life for lanadelumab finished product of 24 months at the recommended long-term storage condition of 5 ± 3 °C is proposed. Other studies further support the proposed shelf life and the suitability of the secondary packaging.

The proposed 24 months storage at long-term conditions (5 ± 3 °C) and the proposed in-use storage up to 14 days ≤ 25 °C are found acceptably supported by data.

The post-approval stability protocol for finished product lots is provided.

2.4.3.5. Adventitious agents

Not applicable. There is no change to the active substance section, the excipients, or the finished product manufacturing process.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The dossier is of good quality and appropriately structured.

The finished product manufacturing process description and process controls are described with a sufficient level of detail and could be considered validated.

The overall strategy to set finished product end-of-shelf-life specification limits is supported and the proposed shelf life of 24 months is considered approvable.

No major objections to the application were identified however some deficiencies have been noted which were appropriately addressed by the Applicant.

2.4.5. 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.

2.4.6. Recommendation(s) for future quality development

Not Applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Non-clinical data have not been submitted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

N/A

2.5.2.2. Secondary pharmacodynamic studies

N/A

2.5.2.3. Safety pharmacology programme

N/A

2.5.2.4. Pharmacodynamic drug interactions

N/A

2.5.3. Pharmacokinetics

N/A

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

N/A

2.5.4.2. Repeat dose toxicity

N/A

2.5.4.3. Genotoxicity

N/A

2.5.4.4. Carcinogenicity

N/A

2.5.4.5. Reproductive and developmental toxicity

N/A

2.5.4.6. Toxicokinetic data

N/A

2.5.4.7. Local tolerance

N/A

2.5.4.8. Other toxicity studies

N/A

2.5.5. Ecotoxicity/environmental risk assessment

Lanadelumab is a recombinant, fully human immunoglobulin subclass 1 (IgG1) kappa light chain monoclonal antibody targeting plasma kallikrein (pKal) and is indicated for routine prevention of recurrent attacks of hereditary angioedema in patients aged 12 years and older. Lanadelumab is a potent inhibitor of the proteolytic activity of active pKal for human, rat, and cynomolgus monkey. The drug substance manufacturing process uses a recombinant Chinese hamster ovary (CHO) cell line grown in suspension culture.

The Applicant has provided a justification for not performing ERA studies. The drug product is composed of naturally occurring amino acids; therefore lanadelumab is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

This application concerns an extension for the expanded use of lanadelumab for routine prophylaxis to prevent attacks and control the symptoms of hereditary angioedema (HAE) in pediatric patients 2 to <12 years of age. TAKHZYRO was first approved for routine prophylaxis to prevent attacks of HAE in patients 12 years and older in the EU on 22 November 2018.

No new nonclinical studies of relevance have been submitted with this extension. However, the Applicant has submitted information on 4 nonclinical studies that have been conducted since submission of the original marketing authorisation application. These additional non-GLP pharmacology and pharmacokinetics studies were conducted to evaluate a different indication with a different route of administration. As they do not provide with new meaningful information for the present extension, they have not been assessed. The following information is selected from the EPAR from the initial marketing authorisation application:

'Repeat-dose studies evaluating once weekly SC injection in both rats (up to 28 days) and cynomolgus monkeys (up to 6 months) evidenced that 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."

The MAH refers to the nonclinical safety studies evaluating SC administration of lanadelumab for up to 6 months in cynomolgus monkeys and considers this to support use in the paediatric patient population aged ≥ 2 to <12 years. The nonclinical program conducted to date indicated no safety signal or toxicity with subcutaneously administered lanadelumab at doses of up to and including the highest tested dose (50 mg/kg, once weekly) for 6 months in cynomolgus monkeys 2.7 to 3.3 years old at initiation of dosing. This corresponds to juvenile (undefined lower limit to 12 years old) to adolescent (12 to 16/18 years old) aged humans (Morford et al, 2011). No specific target organ toxicity or toxicity relevant for developing organ systems was observed in the cynomolgus monkeys. This reasoning is acknowledged, albeit it could be questioned whether cynomolgus monkeys 2.7 to 3.3 years old represent children down to the age of two years.

Further, as part of the application, reference was made to the results from the non-clinical ePPND study on pre- and postnatal developmental toxicity in cynomolgus monkeys. At the maternal dose of 50 mg/kg prior to parturition. the neonates were potentially exposed to lanadelumab through placental transfer in utero, and through breast milk (at 0.20% of maternal plasma concentration), yielding plasma concentrations in neonates exceeded both the IC50 (half-maximal inhibitory concentration) of the IC90 (90% inhibitory concentration) of 18,777 ng/mL for the formation of the cHMWK in a population pharmacokinetics model. The lanadelumab plasma concentration at postnatal Day 90 still exceeds the cHMWK IC50 level. There was not any evidence of adverse maternal or infant findings. The ePPND study in cynomolgus monkeys did not identify lanadelumab-related effects on pregnancy and parturition, embryo foetal development, survival, growth, and/or postnatal development of offspring with a margin of toxicity to NOAEL of 32x. Therefore, an update of the PI is not considered needed.

In accordance with ICH S11, the existing non-clinical data did not identify findings which would warrant additional toxicity studies (i.e., JAS studies) to support the extension to include pediatric patients from the age of 2. The general toxicology studies performed in rats (up to 28 days) and monkey (up to 6 months duration) did not identify any target organs of toxicity and was overall well tolerated.

As regards the environmental risk, lanadelumab is already used in existing marketed products and no significant increase in environmental exposure is anticipated as the drug product is composed of naturally occurring amino acids. Therefore, lanadelumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The extension is approvable from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The MAH 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.

The clinical development program supporting the use of lanadelumab for routine prophylaxis to prevent attacks of HAE in paediatric patients consists of a single pivotal Phase 3 trial as shown below.

Table 2: Overview of clinical studies

Study No.	Study Design	Test Product/Dose Duration	Study Objectives	Subjects Planned/Dosed/Completed	Diagnosis Inclusion Criteria
SHP643-301 (Study Completed 30 Oct 2021)	Open label	150 mg/mL lanadelumab SC injection q2wks for subjects 6 to <12 years[a] q4wks for subjects 2 to <6 years 52-week treatment period: Treatment Period A (26 weeks) and Treatment Period B (26 weeks)	To evaluate the safety, PK, PD, clinical activity/outcomes, and immunogenicity of lanadelumab in children	20/21[b]/20[c]	Type I or II HAE 2 to <12 years ≥1.0 angioedema attack per 3 months (12 weeks)

[a] Subjects 6 to <12 years of age could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion with the sponsor's medical monitor approval, if they were well controlled (eg, attack-free) for 26 weeks with lanadelumab treatment in this study.

[b] Twenty-one subjects received at least 1 dose of lanadelumab and were therefore included in the safety and PK datasets (N=4 subjects aged 2 to <6 years; N=17 subjects aged 6 to <12 years).

[c] One subject (2 to <6 years age group) included in the safety and PK datasets did not complete the 52-week treatment period.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Plasma concentrations of lanadelumab were measured using enzyme-linked immunosorbent assay (ELISA) with a validated range between 3.13 and 400 ng/mL. Serum samples were tested for ADA to lanadelumab using an electrochemiluminescence assay with an assay sensitivity of 46.62 ng/mL. Serum samples were also evaluated for the presence of NAbs to lanadelumab using an electrochemiluminescence assay. Plasma concentrations of cHMWK activity were tested on a Western blot assay and measured on a chemiluminescent Western blot scanner.

ADME

There are no new specific biopharmaceutic studies performed with lanadelumab.

The intended to-be-marketed presentation will be a 1 mL prefilled syringe (PFS), which has an identical product formulation to the study drug used in Study SHP643-301.

Population Pharmacokinetic analysis

The population PK dataset consisted of 278 subjects (3476 post-dose samples), which included 21 (7.6%) paediatric patients with HAE (from study SHP643-301; 4 subjects aged 2 to < 6 years and 17 aged 6 to <12 years) who had at least one PK and PD sample in Study SHP643-301 and were included in the analysis. In addition, 24 (8.6%) healthy subjects (DX-2930-01) and 233 (83.8%) patients with HAE (DX-2930 02, DX-2930-03 and DX-2930-04) were included in the analysis. Study DX-2930-03 and DX-2930-04 included a total of 22 adolescent patients with HAE (unique IDs), respectively, who received at least one dose of lanadelumab. A total of 2.3% of samples were BQL.

A previously developed one-compartment model with linear elimination and first-order rate of absorption (Ka) was used to characterize the concentration-time profiles of lanadelumab. Model parameters were re-estimated, including any covariate effects which were estimated as part of the most recent model. The final model (Table 3) included the effect of body weight of CL/F and V/F using fixed exponents (i.e. 0.75 and 1,

respectively) and the effect of health status (healthy volunteers and patients with HAE) on the CL/F of lanadelumab.

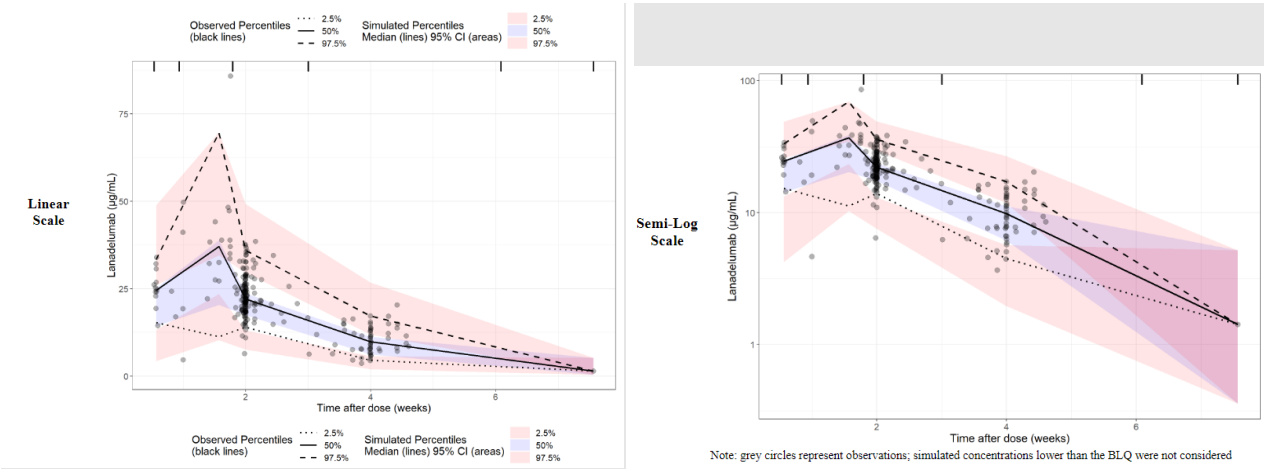
The final population PK model was used to derive post hoc parameters as well as simulate the exposure in children aged 2 -12 years (10-53 kg).

Table 3: Final population PK parameters of Lanadelumab

Parameter (Unit)	Typical Value	Bootstrap (n=250 replicates)		η Shrinkage (%)
		RSE%	Median (2.5% - 97.5% Percentile)	
Fixed Effect				
Ka (h^{-1})	0.0182	8.37	0.0183 (0.0157 - 0.0214)	-
CL/F (L/h)	$0.0256 \times (WT/70)^{0.75}$	2.18	0.0257 (0.0246 - 0.0268)	-
V/F (L)	$12.6 \times (WT/70)^{1.00}$	2.40	12.6 (12.1 - 13.3)	-
Covariate Effect				
Health status on CL/F	× 0.868 if Healthy	6.87	0.867 (0.72 - 0.95)	-
Random Effects				
IIV Ka (%)	69.2	19.6	64.9 (38.9 – 84.2)	48.8
IIV CL/F (%)	28.1	6.92	27.7 (24.3 – 31.7)	10.8
IIV V/F (%)	26.2	10.8	25.7 (21.2 – 30.9)	26.8
Error Model				
Additive Error (ng/mL)	59.9	38.8	59.1 (4.43 - 91.3)	-
Proportional Error (%)	18.8	171.1	18.7 (0.873 - 413)	-

CI = confidence interval; CL/F = apparent clearance; IIV = inter-individual variability (%) approximation, calculated as 100 x sqrt(omega expressed as variance); Ka = first-order absorption rate constant; V/F = apparent volume of distribution; WT = body weight, RSE = relative standard error; NA = not applicable.
Note 1: Population PK parameters are presented for a typical patient of 70 kg with HAE.
Note 2: Of a total of 250 bootstrap runs, a total of 228 (91.2%) runs successfully converged.

Figure 1: Prediction-corrected visual predictive check of lanadelumab concentrations – Study SHP643-301



Special populations

Children

Given the sparsity of the PK sampling, population PK modelling was used to provide post hoc parameter estimates for this study. Body weight was the main identified factor that affects the distribution and elimination lanadelumab. Following lanadelumab administration of 150 mg q2wks in subjects 6 to <12 years, the model-based median [range] time to reach the maximum concentration (Tmax) at steady state was 86 [66-137] hours and the model-based median [range] half-life was 12.6 [9.59-27.3] days. The model-based means (SD) of Cmax,ss, Cmin,ss, and Cavg,ss were 41.6 (14.6), 26.2 (8.76), and 35.2 (11.8), respectively.

Following lanadelumab administration of 150 mg q4wks in subjects 2 to <6 years, the model-based median [range] Tmax at steady state was 122 [108-135] hours and the model-based predicted median [range] half-life was 11.7 [10.2-13.9] days. The model-based means (SD) of Cmax,ss, Cmin,ss, and Cavg,ss were 39.0 (12.1), 12.0 (5.34), and 25.7 (8.92), respectively. Descriptive statistics of steady-state exposure parameters of lanadelumab in both age groups are presented in Table 4.

Table 4: Descriptive Statistics of Steady-State Exposure Parameters of Lanadelumab

Age Group	Statistics	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$C_{avg,ss}$ (µg/mL)	$AUC_{TAU,ss}$ (µg.day/mL)	T_{max} (h)	$t_{1/2}$ (days)
6 to <12 years 150 mg q2wks SHP643-301 (N=17)	Mean	41.6	26.2	35.2	492	90.4	13.5
	SD	14.6	8.76	11.8	165	18.9	3.89
	SE	3.55	2.12	2.85	39.9	4.58	0.944
	CV%	35.2	33.4	33.4	33.4	20.9	28.8
	Geometric Mean	39.0	24.8	33.2	464	88.7	13.2
	Geometric CV%	39.2	37.3	37.7	37.7	20.0	22.7
	Median	43.3	26.5	37.3	522	86.0	12.6
	Min	20.7	12.5	18.3	256	66.0	9.59
	Max	70.8	42.2	54.5	763	137	27.3
2 to <6 years 150 mg q4wks SHP643-301 (N=4)	Mean	39.0	12.0	25.7	719	122	11.9
	SD	12.1	5.34	8.92	250	11.4	1.83
	SE	6.05	2.67	4.46	125	5.69	0.916
	CV%	31.1	44.6	34.7	34.7	9.4	15.5
	Geometric Mean	37.7	11.1	24.6	690	121	11.8
	Geometric CV%	30.1	46.5	34.0	34.0	9.4	15.5
	Median	36.1	10.9	23.7	662	122	11.7
	Min	27.6	6.98	17.3	483	108	10.2
	Max	56.1	18.9	38.2	1070	135	13.9

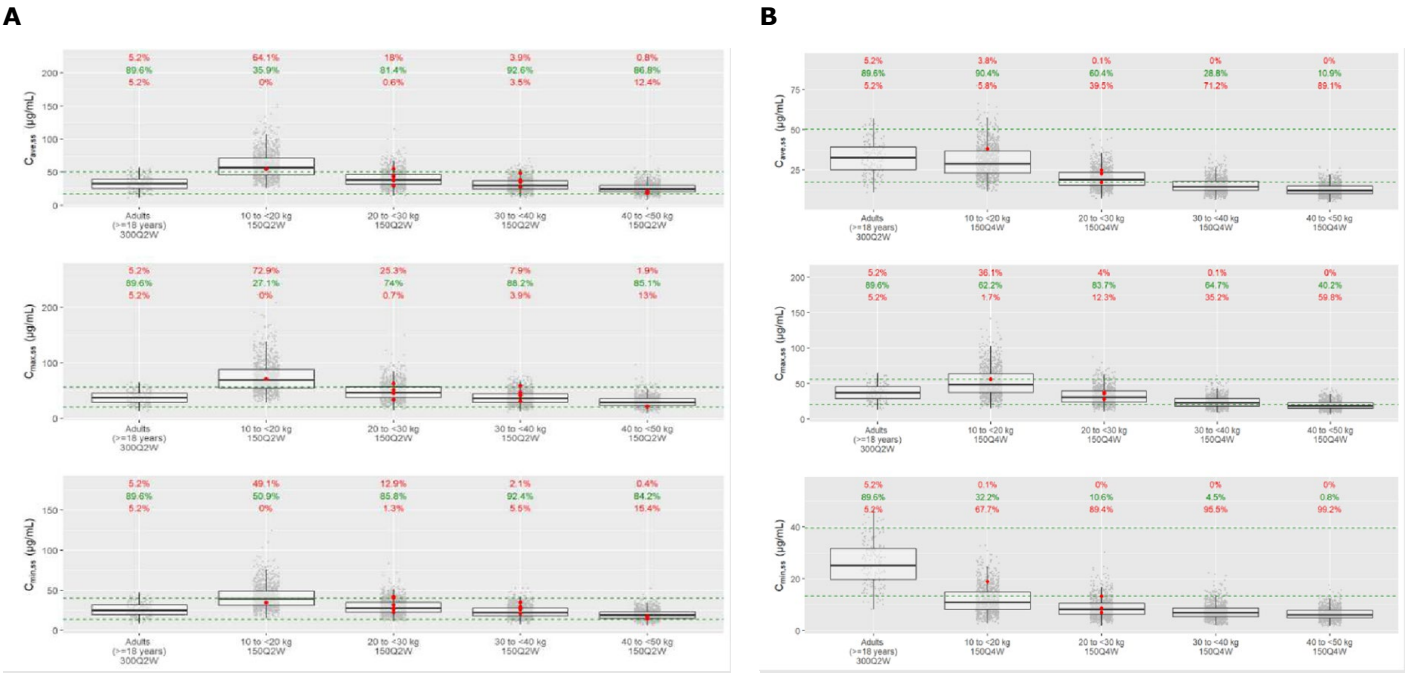
$AUC_{TAU,ss}$=area under the curve over the dosing interval at steady state; $C_{avg,ss}$=average concentration over the dosing interval at steady-state; $C_{max,ss}$=maximum observed concentration at steady state; $C_{min,ss}$=minimum concentration at steady state; CV=coefficient of variation; q2wks=every 2 weeks; q4wks=every 4 weeks; SD=standard deviation; SE=standard error; $t_{1/2}$=elimination half-life; T_{max}=time to maximum concentration

Based on the popPK post hoc parameters, rich concentration-time profiles of lanadelumab for paediatric patients in the population PK analysis were simulated following repeated administration of lanadelumab, and exposure parameters under steady state conditions were derived.

Simulations of posologies stratified on weight category

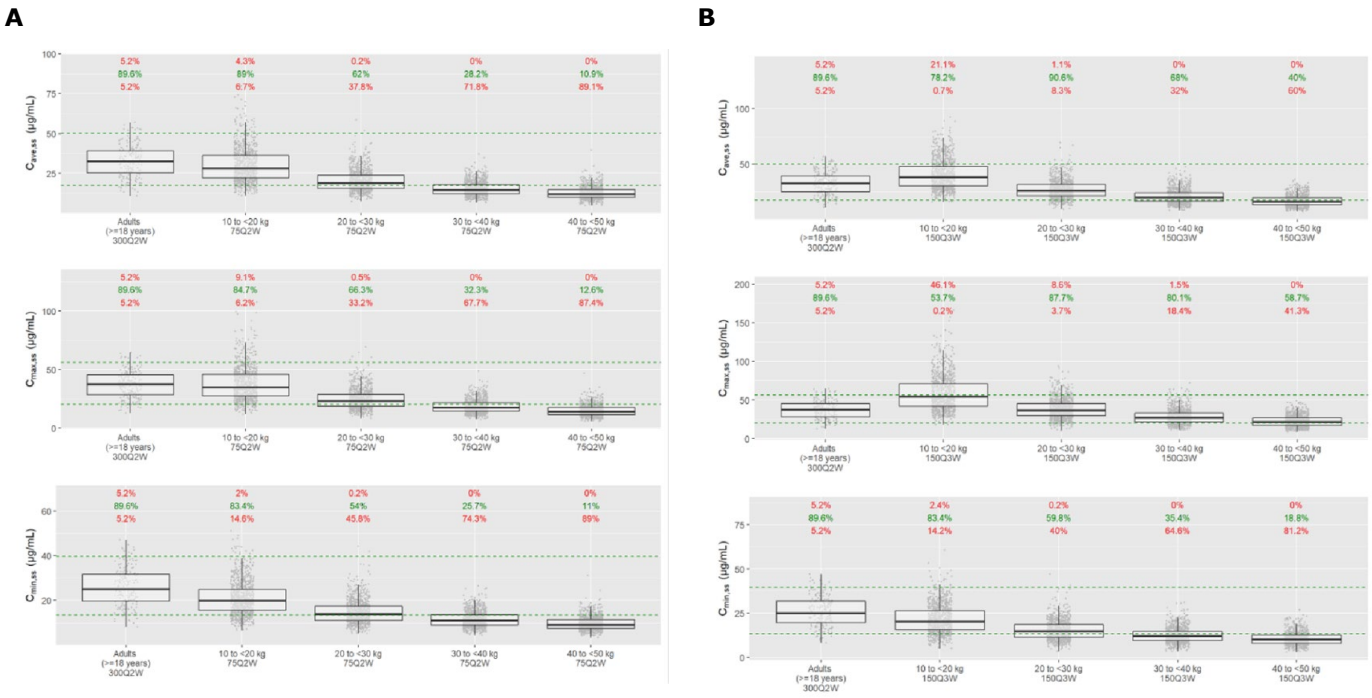
The MAH provided Figure 2 and Figure 3 to compare the simulated exposure parameters in children adult exposure (adults given the approved dose 300 mg Q2W), stratified on weight-bands. In all the simulations provided, no concentration values below limit of quantification (BQL) were omitted.

Figure 2: Virtual Paediatric Patients in Each Weight Category Receiving A. 150 mg Q2W or B. 150 mg Q4W (N=1000 per weight category) compared to adults given 300 mg Q2W



Boxplot for adults is based on data from the actual subjects enrolled in Studies DX 2930-03 and -04 and received 300 mg Q2W (N=192). The lower and upper horizontal green dashed lines are the 5th and 95th percentiles of the reference data (ie, 300 mg Q2W in adults); red numbers represent the percentage above or below the reference range; green numbers represent the percentage within the reference range.

Figure 3: Virtual Paediatric Patients in Each Weight Category Receiving A. 75 mg Q2W or B. 150 mg Q3W (N=1000 per weight category) compared to adults given 300 mg Q2W



Boxplot for adults is based on data from the actual subjects enrolled in Studies DX 2930-03 and -04 and received 300 mg Q2W (N=192). The lower and upper horizontal green dashed lines are the 5th and 95th percentiles of the reference data (ie, 300 mg Q2W in adults); red numbers represent the percentage above or below the reference range; green numbers represent the percentage within the reference range

Pharmacodynamics

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 and Secondary pharmacology

The pharmacodynamic effect in the paediatric study (SHP643-301) was assessed by pKal activity, measured as cleaved high molecular weight kininogen (cHMWK) levels. These levels were used in the pooled population PK/PD modelling analysis.

Plasma kallikrein activity in study SHP643-301 is summarised in Table 5. Corresponding data for the adult/adolescent study DX-2930-03 are given for comparison.

Table 5: Plasma Kallikrein Activity Measured by %cHMWK by Treatment Group and Study Visit (Study SHP643-301 and DX-2930-03) (Summarised by Assessor)

	SHP643-301		DX-2930-03			
	150 mg q4w (N=4)	150 mg q2w (N=17)	Placebo (N=41)	150 mg q4w (N=28)	300 mg q4w (N=29)	300 mg q2w (=27)
Day 0						
n	4	16	41	28	29	27
Mean (SD)	30.2 (13.6)	45.6 (25.8)	49.9 (28.8)	47.7 (27.1)	53.7 (24.5)	48.4 (30.0)
Day 182						
n	3	11	38	27	28	26
Mean (SD)	17.9 (14.3)	18.7 (10.6)	57.4 (25.6)	25.5 (11.8)	25.9 (11.4)	19.5 (9.4)

Relationship between plasma concentration and effect

A population PK/PD analysis based on studies DX-2930-01 (healthy subjects), DX-2930-02 (patients, Multiple Ascending Dose-Study), DX-2930-03 (patients, "HELP" study) and DX-2930-04 ("HELP" extension study) was previously developed based on the 120-safety data cut-off (01-Jan-2018). An indirect-response Imax model was used to model the relationship between lanadelumab concentrations and cHMWK levels (%). This previously developed final model was considered as the new base model for the current analysis, which also included study SHP643-301 (paediatric study). The PK/PD dataset was constructed by including observed concentrations of lanadelumab (PK) and cHMWK levels (%) (PD). The mean Cmin,ss associated with the 150 mg q4w (2 to < 6 years) and 150 mg q2w (6 to < 12 years) dosing were approximately 1.3- and 2.8-fold higher than the model estimated IC50 of cHMWK, respectively.

Exposure-response analysis of efficacy was performed based on data collected in studies DX-2930-03, DX-2930-04 and SHP643-301. For the longitudinal exposure-response analysis, longitudinal secondary exposure parameters (Cmax, Cmin and Cave) (i.e., for each month) were derived with the population PK model. The time to first HAE attack was explored as a function of the Cave,ss of lanadelumab in paediatric subjects (SHP643-301) and non-paediatric subjects (DX-2930-03). Cox-proportional hazard regression models were developed for the probability of a first HAE attack based on Cave,ss and/or Cmin,ss.

Exposure-response analysis of safety was previously performed based on data collected in study DX-2930-03. The data was updated by including data from Study DX-2930-03, Study DX-2930-04 and SHP643-301. An exploratory exposure-response analysis was performed to assess the relationships between steady state exposure to lanadelumab (Cmax,ss, Cmin,ss, and Cave,ss) and selected laboratory parameters. The strength of the relationship was assessed using statistical estimator (r2, slope, and p-value for slope of 0). No significant relationship was noted in this pooled analysis.

2.6.3. Discussion on clinical pharmacology

The purpose of this application is to seek approval for the use of lanadelumab in paediatric patients 2 to <12 years of age for routine prophylaxis to prevent attacks and control the symptoms of HAE. Study SHP346-301 included 21 children aged 2 to <12 years. Data in children aged <5 years is limited (four subjects, 10-20 kg).

There are no indications that the pathogenesis of HAE is different in the paediatric versus the adult and adolescent populations. Therefore, extrapolation of efficacy to the paediatric population using model-based analysis and simulation is considered an acceptable approach. Efficacy in the paediatric population 2 to <12 years was supported by PK exposure matching and extrapolation of efficacy from adolescents and adults. Population PK modeling served as the primary basis of estimating lanadelumab PK parameters (ie, the primary endpoint) for Study SHP643-301.

There is no new information regarding biopharmaceutics and analytical methods relevant to the clinical trial material used in Study SHP643-301.

The analytical methods were previously validated and found acceptable. Lanadelumab plasma concentration data were obtained using an ELISA.

The ADA and NAb assays were clearly described and adequately validated. In the initial MAA, it was agreed that, using either 0.1% or 1% cut-off, presence of neutralising anti-lanadelumab antibodies did not have any apparent effect on lanadelumab exposure, efficacy or reported AEs. All ADAs reported were of low titer. It is agreed to use the 0.1% cut point in the NAb assay instead of the usual 1% rejection threshold.

The intended to-be-marketed presentation will be a 1 mL prefilled syringe (PFS), which has an identical product formulation to the study drug used in Study SHP643-301. The commercial 1 mL PFS presentation will have the same dosage, volume of injection and SC route of administration as the SHP643-301 study drug delivered with a disposable syringe at each injection time point in the study. As the formulation is identical between the two presentations, it is agreed that a dedicated PK study is not required for the transition from the vial product to the PFS product.

The methods used to evaluate the population PK model are adequate. The conducted covariate analysis, and reasoning regarding not re-testing covariate that are known to have significant impact, is supported. The presented goodness-of-fit plots and prediction corrected visual predictive checks indicate that the model can adequately describe the data in the HAE population. It is of importance that the PK in children is adequately described as simulations are required to determine the adequacy of the proposed posology. For children aged ≥2 years of age, it is not expected that factors other than body weight, affect the distribution or elimination of monoclonal antibodies compared to adults.

The BLQ-samples were set to zero in the dataset. The MAH states that overall, 2.3% of all samples were BQL. Children 2 to <6 years have a lower Cmin compared to older children, however, the percent BQL samples was low in children 2-<6 years old as well (2.1%, pre-first dose samples excluded). The model parameters are estimated with low uncertainty. The MAH has presented figures stratified on study, age and body weight which indicate that the model can capture the paediatric data adequately.

The adult target exposure range for different exposure parameters Q2W was based on the post hoc exposures derived from the model-based empirical bayes estimates (EBEs) for HAE subjects enrolled in Studies DX-2930-03 and 04 using the current population PK model that included Study SHP643-301 to derive the EBEs for both adults and children. It is considered not appropriate to change the model used to derive the target exposure, from the model used when the drug was approved in the target population (i.e., when the

B/R was shown to be positive) as the target exposure then becomes a "moving target" with each new population/application. However, the model appears to be similar to the previous model (based on parameter estimation with and without study 301). Therefore, as there is minimal difference between the model developed based on adults and adolescents' data only and the current model, no reanalysis was requested by CHMP.

The MAH compared the simulated and observed exposure in children to the range in adults (≥18 years) from Study DX-2930-03 and -04. The exposure matching consisted of matching the Cavg between adults/adolescents and paediatric subjects based on an exposure-response analysis. However, the conclusions that Cavg is the driving parameter for efficacy including the dosing regimen cannot be determined with certainty with the data submitted and the possible clinical importance of Cmin cannot be dismissed. Therefore, it was concluded that Cmin must also be considered when determining the appropriate posology. To evaluate the appropriateness of the proposed posology, the MAH presented figures comparing the simulated exposure parameters to adult exposure stratified on weight (simulated with uniform weight distribution). The BLQ-concentrations were not removed for any population in the simulations. As weight, rather than age, is the main underlying factor determining the exposure, a dosing based on weight-bands, irrespective of age, has been implemented in the SmPC for children <12 years of age. For subjects aged 12 and older, 300 mg Q2W was already approved, and this recommendation is maintained, however, a starting dose of 150 mg Q2W may be considered if the subjects weigh <40 kg which has also been implemented in section 4.2 of SmPC.

cHMWK was accepted as a pharmacodynamic marker for pKal activity at time of initial marketing authorisation of lanadelumab. In study SHP643-301 at day 182 cHMWK had decreased to 59% of the baseline value in subjects receiving 150 mg q4w and to 40% with 150 q2w. Corresponding values for the adult study DX2930-03 were 40-53% (three dosing levels) and an increase to 115% in the placebo arm. Therefore, the decreased percentage of cHMWK reflects the inhibitory effect of lanadelumab on pKal activity supporting efficacy of lanadelumab.

The MAH pooled the paediatric data with the adult and adolescent data and has conducted a concentration-cHMWK analysis, a concentration-average monthly HAE attacks and time to first HAE attack analysis, and a concentration-safety analysis. One aspect of the exposure-time to first HAE attack model was to assess which exposure parameter drives the efficacy. However, due to several limitations the approval must be based on extrapolation of efficacy from the paediatric data with the data observed in adults and adolescents A PK/PD model to describe the relationship between lanadelumab concentrations and cHMWK levels (%) was developed. The goodness-of-fit indicate that there may be some model misspecification (trend in CWRES vs time plot) and the model maybe does not fully capture the change in %cHMWK over time. The pcVPC indicates a fairly well capture of the decrease of the median cHMWK (%) vs concentration, however, there is a slight overprediction by the model in Study SHP643-301. The model included weight on Kout and health status on Kin (healthy volunteer vs patient). Further, after inclusion of body weight, the MAH investigated age as a covariate; however, as weight was already included in the model and is correlated to age the results are confounded.

The main issue with the exposure-response analysis of HAE attacks model is that patients in study DX-2930-03 received lanadelumab 150 mg q4w, 300 mg q2w and 300 mg q4w. Due to the selected doses in each arm, Cavg and Cmin are expected to be correlated to a considerable degree and it is not possible to differentiate if it is Cavg or Cmin that drives the efficacy. In addition, although Cavg performed better than Cmin based on AIC, the difference in objective function value (OFV) was rather limited. Furthermore, it was concluded by the

MAH that children have fewer HAE attacks compared to adults which may further complicates the analysis and conclusions. This relative difference has not been discussed by the MAH.

In summary, the conclusion that Cavg is the driving parameter for efficacy and that Cmin has no impact on efficacy has not been convincingly demonstrated. Therefore, Cmin should be taken into consideration as a driving PK parameter for efficacy in the exposure-response analysis to determine the posology.

The exposure-safety analysis was conducted by pooling the data from the 21 paediatric patients (<12 years old) with the data from 187 adult and adolescent subjects (unique ID's) and performed a regression analysis of exposure versus selected safety parameters. No significant relationship was noted in this analysis, however, there is a limited number of paediatric subjects limiting the conclusion (see Clinical Safety section).

2.6.4. Conclusions on clinical pharmacology

Due to the rarity of the disease in younger children, the approval is based on extrapolation of efficacy from adults to children using a model-based approach. The population PK model is considered to adequately capture the exposure in children and to be adequate for simulation of exposure to be used for extrapolation.

Body weight is the main covariate with greatest impact on exposure of lanadelumab, and therefore the posology is based on this.

2.6.5. Clinical efficacy

The clinical development program supporting the use of lanadelumab for routine prophylaxis to prevent attacks of HAE in paediatric patients consists of a single Phase 3 trial (Table 6)

Table 6: Overview of Clinical Efficacy Study

Study ID (Study Status)	Study Design	Test Product/ Dose/ Duration	Study Objectives	Number of Subjects Planned/ Enrolled/ Completed	Diagnosis/ Inclusion Criteria
SHP643-301 (LPLV on 30 Oct 2021)	Open-label, multicenter	150 mg/mL lanadelumab SC injection/ q2wks for subjects 6 to <12 years[a] q4wks for subjects 2 to <6 years/ 52 week treatment period: Treatment Period A (26 weeks) and Treatment Period B (26 weeks)	To evaluate the safety, PK, PD, clinical activity/outcomes, and immunogenicity of lanadelumab in children	20/21/20	Type I or II HAE/ 2 to <12 years ≥1.0 angioedema attack per 3 months (12 weeks)

HAE=hereditary angioedema; ID=identification; LPLV=last patient last visit; PD=pharmacodynamics; PK=pharmacokinetics; q2wks=every 2 weeks; q4wks=every 4 weeks; SC=subcutaneous

[a] Subjects 6 to <12 years of age could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion with the sponsor's medical monitor approval, if they were well controlled (eg, attack-free) for 26 weeks with lanadelumab treatment in this study.

2.6.5.1. Dose response study(ies)

No separate dose response studies in the paediatric population were performed. Dose regimens were based on the population PK modelling and simulation. Please refer to clinical pharmacology section above for further information.

2.6.5.2. Main study(ies)

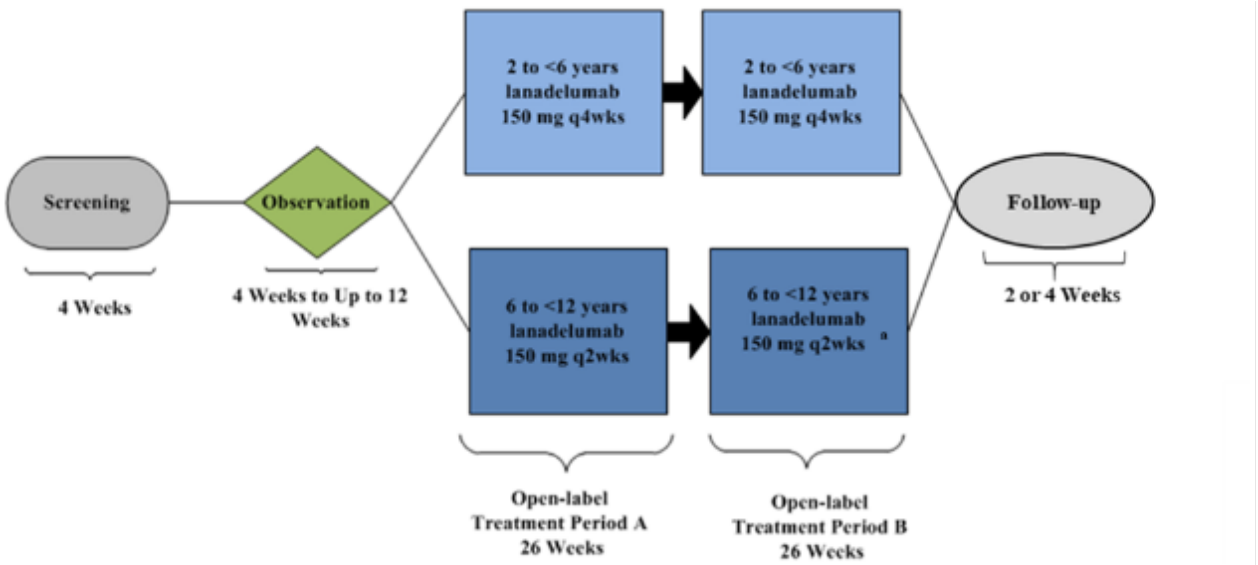
Title of study

Study SHP643-301: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lanadelumab for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) in Pediatric Subjects 2 to <12 years of Age (SPRING STUDY)

Methods

Study SHP643-301 was an open-label, multicentre study (Figure 4)

Figure 4: Study Design Schematic



q2wks=every 2 weeks; q4wks=every 4 weeks

[a] An individual subject's dose frequency could be modified based on a benefit-risk assessment and recommendation from the treating physician. Consultation with and approval by the sponsor's medical monitor were required. For example, subjects 6 to <12 years of age may administer lanadelumab 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they are well controlled (eg, attack-free) for 26 weeks with lanadelumab treatment in this study.

Subjects who experienced ≥1 angioedema attack during the observational period and who remained eligible per study criteria were to enter the lanadelumab treatment period for 52 weeks. Subjects were to stay in the observation period for a minimum of 4 weeks, but the observational period could be prolonged up to 12 weeks if necessary. Subjects who reported more than 2 HAE attacks (confirmed by the investigator and agreed with the sponsor's medical monitor) within the first 2 weeks of the observation period could exit the observational period and enter the treatment period early.

The attack rate in the observation period served as the baseline for the study.

- **Study Participants**

Main eligibility criteria included paediatric patients (2 to <12 years) of both sexes with a diagnosis of HAE (Type I or II) and a historical baseline HAE attack rate of ≥1.0 angioedema attack per 3 months (12 weeks).

- **Treatments**

The lanadelumab dose regimens were:

- 150 mg q2wks for subjects 6 to <12 years old; total of 27 doses administered over the 52-week treatment period.
- 150 mg q4wks for subjects 2 to <6 years old; total of 14 doses administered over 52-week treatment period

Subjects 6 to <12 years of age could switch to a dosing regimen of 150 mg q4wks in Treatment Period B at the investigator's discretion and sponsor's medical monitor approval, if they were well controlled (e.g., attack-free) for 26 weeks with lanadelumab treatment in this study.

The fixed age-based dosing regimens in Study SHP643-301 were selected based on population PK simulations using a model generated from adult data. For details, please refer to the Pharmacokinetic section.

The new pre-filled syringe with 150 mg lanadelumab in 1 ml for paediatric use under assessment in the current procedure was not used during the study. Instead, a ready-to-use solution with a lanadelumab concentration of 150 mg/mL provided in a single-use 2-mL glass vial (150 mg/ 1 mL) identical to the commercially available product was used.

Acute HAE attacks during the study were to be managed in accordance with the investigator's usual care of their patients, including use of individualized acute therapy that the investigator deemed as medically appropriate. Use of C1-INH was permitted as acute therapy but not as long-term prophylaxis. Short-term prophylactic treatment for HAE was permitted if medically indicated, i.e., to avoid angioedema complications from medically indicated procedures.

- **Objectives**

The primary objective of this study was to evaluate the safety and PK of lanadelumab in paediatric subjects (2 to <12 years of age) with HAE. Efficacy was a secondary objective.

- **Outcomes/endpoints**

- <u>Safety (primary endpoint)</u>
    - Adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs).
    - Clinical laboratory testing (haematology, clinical chemistry, and coagulation).
    - Vital signs including blood pressure, heart rate, body temperature, and respiratory rate.
- <u>Pharmacokinetics (primary endpoint)</u>
    - Plasma concentrations of lanadelumab obtained during the study.
    - Pharmacokinetic parameters in plasma, by age group, estimated by a population modelling and simulation approach.

- Efficacy (secondary endpoint)
    - Normalized number of investigator-confirmed HAE attacks for the Overall Treatment period (Day 0 through Day 364).
    - Other clinical outcomes endpoints were also assessed in this study:
        - Normalized number of investigator-confirmed HAE attacks for each efficacy evaluation period other than the Overall Treatment period.
        - Time to the first attack, ie, duration that a subject was attack-free until their first attack for each efficacy evaluation period.
        - Normalized number of investigator-confirmed HAE attacks requiring acute therapy use for each efficacy evaluation period.
        - Normalized number of moderate or severe investigator-confirmed HAE attacks for each efficacy evaluation period.
        - Normalized number of high-morbidity investigator-confirmed HAE attacks for each efficacy evaluation period.
        - Characteristics of investigator-confirmed HAE attacks for each efficacy evaluation period, including duration, severity, attack location, and rescue medication use.
        - Achievement of attack-free status for each efficacy evaluation period.
- Pharmacodynamics
    - Plasma kallikrein (pKal) activity (measured as cleaved high molecular weight kininogen [cHMWK] levels).
- Immunogenicity
    - Measured by presence or absence of neutralizing or non-neutralizing antidrug antibody (ADA) in plasma.
- Exploratory Objectives
    - To evaluate the effect of lanadelumab on health-related quality of life (HRQoL).
    - To evaluate the effect of lanadelumab on C1-INH, complement 4 (C4), and exploratory biomarker(s) of angioedema disease-state bioactivity.

Clinical outcome endpoints were evaluated for the following 5 efficacy evaluation periods:

- Overall Treatment Period (Day 0 through Day 364),
- Treatment Period A (Day 0 through Day 182),
- Treatment Period B (Day 183 through Day 364),
- Overall presumed steady-state period (Day 70 through Day 364),
- Presumed steady-state period for Treatment Period A (Day 70 through Day 182).

- **Sample size**

The sample size for this paediatric study was driven by feasibility considerations as enrolment of paediatric subjects 2 to <12 years old was expected to be difficult. The primary emphasis was to assess the safety and PK of lanadelumab in this age group but also to generate data on clinical outcomes if subjects had sufficient baseline attack frequency for evaluation.

At least 20 paediatric subjects (2 to <12 years of age) with at least 5 subjects in each age group of 2 to <9 years of age and 9 to <12 years of age were planned for enrolment to ensure that a minimum of 15 subjects complete 1 year (52 weeks) of treatment on the study.

- **Randomisation and Blinding (masking)**

Not applicable since the study was single-armed and open-label.

- **Statistical methods**

Due to the limited population and the lack of comparator in the study, only descriptive statistics applied.

All safety and efficacy analyses were based on the safety set, which was defined as all subjects who received any dose of lanadelumab

Results

- **Participant flow**

Table 7: Subject Disposition by Treatment Group (Screened Set)

	Lanadelumab 150 mg q4wks[a] n (%)	Lanadelumab 150 mg q2wks[a] n (%)	Total n (%)
Screened set[b]			24
Screen failures[c]			3
Safety set[d]	4	17	21
Pharmacokinetic set[e]	4	17	21
Pharmacodynamic set[f]	4	17	21
Completed at least 3 months[g]	3 (75.0)	17 (100.0)	20 (95.2)
Completed Treatment Period A[h]	3 (75.0)	17 (100.0)	20 (95.2)
Completed Treatment Period B[i]	3 (75.0)	17 (100.0)	20 (95.2)
Completed study[j]	3 (75.0)	17 (100.0)	20 (95.2)
Prematurely discontinued study	1 (25.0)	0	1 (4.8)
Primary reason for study withdrawal			
Withdrawal by parent/guardian	1 (25.0)	0	1 (4.8)

q2wks=every 2 weeks; q4wks=every 4 weeks
a Subjects were included based on their original treatment assignment.
b Screened subjects consisted of all subjects who have signed an informed consent document.
c Screen failures consisted of all screened subjects who were not enrolled.
d The safety set consists of all subjects who received lanadelumab.
e The pharmacokinetic set was defined as all subjects in the safety set who have at least 1 evaluable postdose pharmacokinetic concentration value.
f The pharmacodynamic set was defined as all subjects in the safety set who have at least 1 evaluable postdose pharmacodynamic value.
g The at least 3 months completion was defined as subject completed the visit on or after Visit 12 (Week 12).
h Treatment Period A completion was defined as subject completed the Visit 26 (Week 26).
i Treatment Period B completion was defined as subject completed the Visit 52 (Week 52).
j Study completion electronic case report form was used to determine subject completion status.
Note: Percentages of subjects are based on all subjects in the safety set.

A girl (age cohort 2-<6 years) discontinued the study prematurely at day 32 due to withdrawal by the parent/guardian.

- **Recruitment**

The study period was 19 Aug 2019 (first subject enrolled) to 30 Oct 2021 (last subject completed).

Participants were recruited from 17 centres across 5 countries (US, Canada, Spain, Hungary, and Germany).

- **Conduct of the study**

Protocol deviations

All subjects reported at least one protocol deviation. Three major protocol deviations were reported: Subject entered Observation Period prior to signing the new ICF (1), Subject was not reconsented in a timely manner (1), PK and ADA samples were lost in transit and never reached to PPD labs (1).

Protocol amendments

There were four protocol amendments to the original protocol, summarised below.

Table 8: Protocol amendments Study SHP643-301

Protocol SHP643-301	Date	Global/Country/Site Specific
Original Protocol	06 May 2019	Global
Protocol Amendment 1.0	12 Aug 2019	Global
Protocol Amendment 1.1	15 Oct 2019	Germany
Protocol Amendment 1.2	05 Dec 2019	Germany
Protocol Amendment 2.0	22 Jun 2021	Global

The protocol amendments included revision of self-administration instructions, clarifications of maximum duration of study participations and follow-up period, and removal of an interim analysis summarising data up to Treatment Period A as well as smaller amendments of eligibility criteria.

- **Baseline data**

Table 9: Demographics and Baseline Characteristics (Safety Set) (Truncated by Assessor)

Characteristics	Lanadelumab 150 mg q4wks[a] (N=4)	Lanadelumab 150 mg q2wks[a] (N=17)	Total (N=21)
Age (years)[b]			
n	4	17	21
Mean (SD)	4.45 (0.843)	8.68 (1.391)	7.88 (2.134)
Median	4.50	8.90	8.70
Min, max	3.5, 5.3	6.0, 10.9	3.5, 10.9
Age Group 1 – n (%)			
2 to <6 years	4 (100.0)	0	4 (19.0)
6 to <12 years	0	17 (100.0)	17 (81.0)
Sex – n (%)			
Male	2 (50.0)	7 (41.2)	9 (42.9)
Female	2 (50.0)	10 (58.8)	12 (57.1)
Geographic Region – n (%)			
US	1 (25.0)	12 (70.6)	13 (61.9)
Canada	1 (25.0)	1 (5.9)	2 (9.5)
Europe	2 (50.0)	4 (23.5)	6 (28.6)
Race Group – n (%)			
White	4 (100.0)	16 (94.1)	20 (95.2)
Other	0	1 (5.9)	1 (4.8)
Weight (kg)			
n	4	17	21
Mean (SD)	20.35 (3.246)	34.69 (12.482)	31.96 (12.630)
Median	21.05	31.05	29.93
Min, max	15.8, 23.5	19.6, 63.3	15.8, 63.3
Prior long-term prophylactic treatment[e] – n (%)			
Yes	0	5 (29.4)	5 (23.8)
No	4 (100.0)	12 (70.6)	16 (76.2)
LTP therapy use[f] – n (%)			
C1-INH	1 (25.0)	2 (11.8)	3 (14.3)
Androgens	0	0	0
Antifibrinolytics	0	0	0
Not on LTP	3 (75.0)	15 (88.2)	18 (85.7)

Table 10: Baseline HAE Attack History (Safety Set)

Characteristics	Lanadelumab 150 mg q4wks[a] (N=4)	Lanadelumab 150 mg q2wks[a] (N=17)	Total (N=21)
Age at onset of angioedema symptoms (years)			
n	4	17	21
Mean (SD)	2.0 (1.41)	3.5 (2.85)	3.2 (2.68)
Median	1.5	3.0	2.0
Min, max	1, 4	0, 9	0, 9
HAE type – n (%)			
Type I	4 (100.0)	16 (94.1)	20 (95.2)
Type II	0	0	0
Unspecified-Type I or Type II	0	1 (5.9)	1 (4.8)
History of laryngeal attacks – n (%)			
Yes	1 (25.0)	4 (23.5)	5 (23.8)
No	3 (75.0)	13 (76.5)	16 (76.2)
Primary attack locations[b] – n (%)			
Peripheral	2 (50.0)	5 (29.4)	7 (33.3)
Abdominal	2 (50.0)	11 (64.7)	13 (61.9)
Laryngeal	0	1 (5.9)	1 (4.8)
Historical number of attacks in the last month			
n	4	17	21
Mean (SD)	2.8 (2.06)	1.9 (2.25)	2.1 (2.19)
Median	3.0	1.0	1.0
Min, max	0, 5	0, 8	0, 8
Historical number of attacks in the last 3 months			
n	4	17	21
Mean (SD)	4.8 (4.35)	4.3 (3.08)	4.4 (3.23)
Median	3.5	4.0	4.0
Min, max	1, 11	0, 13	0, 13
Historical number of attacks in the last 12 months			
n	4	17	21
Mean (SD)	17.0 (24.01)	15.2 (12.64)	15.5 (14.66)
Median	5.5	15.0	12.0
Min, max	4, 53	1, 56	1, 56
Average severity of HAE attacks in the last 12 months – n (%)			
Mild	1 (25.0)	1 (5.9)	2 (9.5)
Moderate	3 (75.0)	13 (76.5)	16 (76.2)
Severe	0	3 (17.6)	3 (14.3)
Average duration of HAE attacks in the last 12 months (days)			
n	4	17	21
Mean (SD)	1.8 (0.96)	2.9 (4.26)	2.7 (3.85)
Median	1.5	2.0	2.0
Min, max	1, 3	1, 19	1, 19
Baseline HAE attack rate (attacks/month)[c]			
n	4	17	21
Mean (SD)	1.86 (1.033)	1.84 (1.645)	1.84 (1.525)
Median	1.72	1.12	1.44
Min, max	0.8, 3.3	0.6, 6.7	0.6, 6.7
Baseline HAE attack rate group (attacks/month)[c] – n (%)			
>0 to <1	1 (25.0)	8 (47.1)	9 (42.9)
1 to <2	2 (50.0)	5 (29.4)	7 (33.3)
2 to <3	0	2 (11.8)	2 (9.5)
≥3	1 (25.0)	2 (11.8)	3 (14.3)

- **Numbers analysed**

The safety set was used for all efficacy and safety analyses. All 21 subjects were included in the Safety set.

- **Outcomes and estimation**

Normalised Number of Investigator-confirmed HAE Attacks

Table 11: Summary of Normalized Number of Investigator-confirmed HAE Attacks by Treatment Group During Overall Treatment Period (Truncated by Assessor)

	Lanadelumab 150 mg q4wks[a] (N=11)			Lanadelumab 150 mg q2wks[a] (N=18)			Total (N=21)		
Parameter Period Statistic	Actual Value	Change From Baseline	Percent Change From Baseline	Actual Value	Change From Baseline	Percent Change From Baseline	Actual Value	Change From Baseline	Percent Change From Baseline
HAE Attack Rate (attacks/month)[b]									
Baseline Observation Period									
n	11			18			21		
Mean (SD)	1.45 (0.790)			1.91 (1.631)			1.84 (1.525)		
Median	1.12			1.28			1.44		
Min, max	0.6, 3.3			0.6, 6.7			0.6, 6.7		
Overall Treatment Period									
n	11	11	11	18	18	18	21	21	21
Mean (SD)	0.07 (0.219)	-1.38 (0.640)	-97.98 (6.715)	0.08 (0.157)	-1.83 (1.607)	-94.43 (15.531)	0.08 (0.170)	-1.76 (1.489)	-94.78 (14.606)
Median	0.00	-1.12	-100.00	0.00	-1.20	-100.00	0.00	-1.28	-100.00
Min, max	0.0, 0.7	-2.5, -0.6	-100.0, -77.7	0.0, 0.5	-6.5, -0.3	-100.0, -34.8	0.0, 0.5	-6.5, -0.3	-100.0, -34.8

Table 12: Summary of Normalized Number of Investigator-confirmed HAE Attacks by Treatment Group During Treatment Period A (Truncated by Assessor)

	Lanadelumab 150 mg q4wks[a] (N=4)			Lanadelumab 150 mg q2wks[a] (N=17)			Total (N=21)		
Parameter Period Statistic	Actual Value	Change From Baseline	Percent Change From Baseline	Actual Value	Change From Baseline	Percent Change From Baseline	Actual Value	Change From Baseline	Percent Change From Baseline
HAE Attack Rate (attacks/month)[b]									
Baseline Observation Period									
n	4			17			21		
Mean (SD)	1.86 (1.033)			1.84 (1.645)			1.84 (1.525)		
Median	1.72			1.12			1.44		
Min, max	0.8, 3.3			0.6, 6.7			0.6, 6.7		
Treatment Period A									
n	4	4	4	17	17	17	21	21	21
Mean (SD)	0.15 (0.308)	-1.71 (0.769)	-95.27 (9.450)	0.08 (0.207)	-1.75 (1.625)	-93.40 (22.975)	0.10 (0.222)	-1.75 (1.484)	-93.76 (20.887)
Median	0.00	-1.72	-100.00	0.00	-1.12	-100.00	0.00	-1.44	-100.00
Min, max	0.0, 0.6	-2.6, -0.8	-100.0, -81.1	0.0, 0.8	-6.4, 0.0	-100.0, -5.1	0.0, 0.8	-6.4, 0. 0	-100.0, -5.1

For both Table 11 and Table 12:
HAE=hereditary angioedema; max=maximum; min=minimum; q2wks=every 2 weeks; q4wks=every 4 weeks; SD=standard deviation.
a The actual treatment received during the given study period.
b The investigator-confirmed HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the given study period divided by the number of days the subject contributed to the period multiplied by 28 days. The investigator-confirmed HAE attack rate during the baseline observation period was the baseline HAE attack rate.
Notes: A month was defined as 28 days.

The Number of Investigator-confirmed HAE Attacks results for Treatment Period B (Day 183 through Day 364), an overall presumed steady-state period (Day 70 through Day 364) and presumed steady-state period for Treatment Period A (Day 70 through Day 182) were consistent with the data from the Overall Treatment Period (primary efficacy analysis).

*Table 13: Summary of Normalized Number of Investigator-Confirmed HAE Attack Rate **Age Group 2-<6** years During **Overall Treatment Period** (table summarised by Assessor from table 14.2.1.1.19)*

	Lanadelumab 150 mg Every 4 Weeks** (N=4)		
Parameter Period Statistic	Actual value	Change from baseline	Percent change from baseline
HAE Attack Rate (attacks/month)			
Baseline Observation Period			
n	4		
Mean (SD)	1.86 (1.03)		
Median	1.72		
Min. Max	0.8, 3.3		
Overall Treatment Period			
n	4	4	4
Mean (SD)	0.18 (0.36)	-1.68 (0,73)	-94,4 (11.1)
Median	0.0	-1.72	-100
Min. Max	0.0, 0.7	-2.5, -0.8	-100, -77.7)

** One subject discontinued treatment at Day 32 and one subjects switched to q2wks dosing due to poor efficacy.

Characteristics of Investigator-confirmed HAE Attacks

The mean (SD) investigator-confirmed HAE attack duration (excluding no attacks) was 15.05 (16.540) hours during the Overall Treatment period, compared to 29.8 (22.01) hours during the baseline observation period.

The mean (SD) HAE attack severity (categorized as 1=mild, 2=moderate, and 3=severe) was 1.99 (0.397) (excluding no attacks) during the Overall Treatment period, compared to 1.70 (0.404) during the baseline observation period.

The most frequent maximum HAE attack severity was no attack during the Overall Treatment period (16 [76.2%] subjects), compared to moderate during the baseline observation period (14 [66.7%] subjects). One subject experienced a severe HAE attack during the study treatment period compared to 3 subjects during the baseline observation period.

Time to First Attack

During the Overall Treatment period, 5 (23.81%) subjects had an investigator-confirmed HAE attack. The median time to first investigator-confirmed HAE attack was not calculable, because less than 50% of subjects experienced attacks during the given study period.

Achievement of Attack-free Status

Table 14: Achievement of Investigator-confirmed HAE Attack-free During Efficacy Evaluation Period (Safety Set) (Truncated by Assessor)

Parameter Statistic	Lanadelumab 150 mg q4wks[a] (N=11)	Lanadelumab 150 mg q2wks[a] (N=18)	Total (N=21)
Overall Treatment Period – N'	11	18	21
Number of subjects with attack-free percentage of attack-free days	10 (90.9)	13 (72.2)	16 (76.2)
n	11	18	21
Mean (SD)	99.72 (0.937)	99.53 (0.983)	99.53 (0.980)
Median	100.00	100.00	100.00
Min, max	96.9, 100.0	96.4, 100.0	96.4, 100.0

Five subjects had 23 investigator-confirmed HAE attacks (1 [9.1%] subject with 5 HAE attacks in the q4wks group and 5 [27.8%] subjects with 18 HAE attacks in the q2wks group). Two of the 5 subjects who had HAE attacks had events that required rescue medication. For the majority of events (22 events), the subjects did not require supportive treatment; 1 event required antiemetic as supportive treatment.

- **Summary of main efficacy results**

The following Table 15 summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). It should be noted that efficacy was not a primary objective in the study.

Table 15: Summary of efficacy for trial SHP643-301 (provided by Applicant, modified by Assessor)

Title: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lanadelumab for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) in Pediatric Subjects 2 to <12 years of Age (SPRING STUDY)		
Study identifier	SHP643-301 EudraCT number: 2018-002093-42 NCT04070326	
Design	This was a Phase 3, open-label, uncontrolled multicentre study to evaluate the safety, PK, PD, and clinical outcomes.	
	Duration of main phase:	52 weeks (Treatment Period A: 26 Weeks, Treatment Period B: 26 Weeks)
	Duration of Run-in phase:	4-12 Weeks
	Duration of Extension phase:	Not applicable
Hypothesis	Not applicable	

Title: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lanadelumab for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) in Pediatric Subjects 2 to <12 years of Age (SPRING STUDY)			
Study identifier	SHP643-301 EudraCT number: 2018-002093-42 NCT04070326		
Treatments groups	Lanadelumab 150 mg every fourth week (q4w)		Original Treatment Assignment: N=4 for subjects aged 2-<6 years Actual Treatment Received During the Overall Study Periods: N=11 including N=7 dosing modified to this regimen.
	Lanadelumab 150 mg every second week (q2w)		Original Treatment Assignment: N=17 for subjects aged 6-<12 years Actual Treatment Received During the Overall Study Period: N=18 including N=1 dosing modified to this regimen
Endpoints and definitions	Secondary endpoint	HAE attack rate	Change in normalized number of investigator-confirmed HAE attacks for the Overall Treatment period (mean attacks/month [SD]) (main efficacy outcome)
	Secondary endpoint	Attack-free	Number (%) of subjects without HAE attacks during Overall Treatment period
Database lock	14 January 2022		

Results and Analysis

Analysis description	**Secondary Analysis**		
Analysis population and time point description	Efficacy analyses were based on the safety set. No comparative analyses were performed.		
	Treatment group	**Lanadelumab 150 mg q4wks[a]**	**Lanadelumab 150 mg q2wks[a]**
	Number of subjects	11	18
	Investigator-confirmed HAE attacks by treatment group during Overall Treatment period		
	Baseline HAE Attack Rate [b]	1.45 (0.790)	1.91 (1.631)
	Change from baseline in HAE Attack Rate	-1.38 (0.640)	-1.83 (1.607)
	Number of Attack-free subjects		
	Baseline	0 [0]	0 [0]
	Overall Treatment period	10 [91]	13 [72]

Title: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Lanadelumab for Prevention Against Acute Attacks of Hereditary Angioedema (HAE) in Pediatric Subjects 2 to <12 years of Age (SPRING STUDY)	
Study identifier	SHP643-301 EudraCT number: 2018-002093-42 NCT04070326
Notes	[a] The actual treatment received during the given study period [b] The investigator-confirmed HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the given study period divided by the number of days the subject contributed to the period multiplied by 28 days. The investigator-confirmed HAE attack rate during the baseline observation period was the baseline HAE attack rate.

2.6.5.3. Clinical studies in special populations

Not applicable since the study population is selected to extend the indication to younger children.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The MAH has provided a comprehensive tabulation comparing the results from the pivotal study in adults/adolescents (DX-2930-03), the supportive open label extension (DX-2930-04) and the paediatric study (SHP643-301) (Table 16).

Table 16: Number of Investigator-confirmed HAE Attacks During the Baseline and Treatment Periods of Studies DX-2930-03, DX-2930-04, and SHP643-301 by Treatment

Study DX-2930-03 (Pivotal Efficacy Study) ITT Population			**Study DX-2930-04 (Supportive Efficacy Study)**						**Study SHP643-301 (Pediatric Study) Safety Population**		
			Rollover Safety Population			**Nonrollover Safety Population**					
Treatment	**Run-in Period[a]**	**Treatment Period**	**Current Treatment[d] (Prior Treatment)[e]**	**Run-in Period[a]**	**Treatment Period**	**Current Treatment[d] (Prior Treatment)**	**Baseline Period[b]**	**Treatment Period**	**Treatment[f]**	**Baseline Observation Period**	**Overall Treatment Period**
	Mean (SD) HAE Attack Rate[c]			**Mean (SD) HAE Attack Rate[c]**			**Mean (SD) HAE Attack Rate[c]**			**Mean (SD) HAE Attack Rate[g]**	
Placebo (N=41)	4.02 (3.265)	2.46 (2.079)	Lanadelumab 300 mg q2wks (Placebo) (N=33)	3.81 (2.997)	0.34 (0.850)	Lanadelumab 300 mg q2wks (No LTP Use) (N=39)	2.61 (2.838)	0.13 (0.290)			
Lanadelumab 150 mg q4wks (N=28)	3.22 (1.830)	0.48 (0.627)	Lanadelumab 300 mg q2wks (150 mg q4wks) (N=26)	3.18 (1.739)	0.20 (0.329)	Lanadelumab 300 mg q2wks (C1-INH Only) (N=53)	2.72 (2.919)	0.30 (0.663)	Lanadelumab 150 mg q2wks (N=18)	1.91 (1.631)	0.08 (0.157)
Lanadelumab 300 mg q4wks (N=29)	3.71 (2.507)	0.60 (0.801)	Lanadelumab 300 mg q2wks (300 mg q4wks) (N=25)	3.54 (2.580)	0.32 (0.494)	Lanadelumab 300 mg q2wks (Oral Therapy) (N=9)	1.47 (1.157)	0.15 (0.325)			
Lanadelumab 300 mg q2wks (N=27)	3.52 (2.327)	0.31 (0.505)	Lanadelumab 300 mg q2wks (300 mg q2wks) (N=25)	3.47 (2.392)	0.19 (0.409)	Lanadelumab 300 mg q2wks (C1-INH & Oral Therapy) (N=2)	1.69 (0.217)	0.15 (0.171)	Lanadelumab 150 mg q4wks (N=11)	1.45 (0.790)	0.07 (0.219)

C1-INH=C1 esterase inhibitor; CSR=clinical study report; HAE=hereditary angioedema; ITT=intent-to-treat; LTP=long-term prophylaxis; N=number of subjects in a group; q2wks=every 2 weeks; q4wks=every 4 weeks; SD=standard deviation

a Run-in period in Study DX-2930-03=baseline for subject in Study DX-2930-03 and for the rollover subjects in Study DX-2930-04.
b Baseline period was for the nonrollover subjects in Study DX-2930-04. Baseline attack rate was 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.
c Attack rate=attacks/month; a month was defined as a 4-week period or 28 days. The DX-2930-04 treatment period investigator-confirmed HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the regular dosing stage of the DX-2930-04 treatment period divided by the number of days the subject contributed to the regular dosing stage of the treatment period multiplied by 28 days. Regular dosing stage for rollover safety population started on the date/time of the second lanadelumab dose.
d Lanadelumab 300 mg q2wks is the open-label dose administered in Study DX-2930-04.
e Prior treatment for rollover safety population is the treatment received in Study DX-2930-03.
f Subject numbers reflect the actual treatment regimen received; due to dose modifications in Treatment Period B, some subjects were treated with both dosing regimens and were counted in each treatment regimen.
g Attack rate=attacks/month; a month was defined as 28 days. In Study SHP643-301, the investigator-confirmed HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the given study period divided by the number of days the subject contributed to the period multiplied by 28 days. The investigator-confirmed HAE attack rate during the baseline observation period was the baseline HAE attack rate.

The treatment period in Study DX-2930-03 was 182 days compared to the 364 days in the Overall Treatment period of study SHP643-301.

2.6.5.6. Supportive study(ies)

N/A

2.6.6. Discussion on clinical efficacy

Takhzyro was approved in 2018 in the EU for routine prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older. As per January 2023, beside Takhzyro two products, the C1-inhibitor Cinryze and the pKal inhibitor Orladeyo, are indicated for routine prophylaxis of HAE in the EU. For this indication, Cinryze is approved from the age of 6 years and Orladeyo from the age of 12 years.

The scopes of the current application are to extend the indication for Takhzyro to paediatric subjects from the age of two years and to include the 150 mg in 1 ml pre-filled syringe as a new strength for paediatric use.

Design and conduct of clinical studies

The pivotal study for the paediatric indication, Study SHP643-301, was an open-label, multicentre study, uncontrolled study. The study design was in accordance with the PIP.

At the time of the orphan designation (2015), HAE was reported to affect less than 0.5 in 10,000 people in the European Union (EU). Furthermore, angioedema episodes usually begin between 5 and 11 years of age (Farkas 2010), leading to diagnosis a couple of years later. The number of paediatric subjects eligible for the study was thus limited.

Main eligibility criteria included paediatric patients (2 to <12 years) of both sexes with a diagnosis of HAE (Type I or II) and a historical baseline HAE attack rate of ≥1 angioedema attack per 3 months.

The baseline HAE attack rate was evaluated during a run-in period of 4-12 weeks. To be eligible to enter the treatment period, subjects were to have a baseline attack rate of at least one attack per 4 weeks. Subjects with frequent attacks could exit the run-in period early. The decision to start treatment before the end of the four-week run-in period may overestimate the baseline HAE attack rate. Upon request, the MAH has clarified that no subject exited the run-in period early, i.e., before the end of the protocol-defined 4-week run-in.

In the pivotal study for marketing authorisation of Takhzyro in adults and adolescents, Study DX-2930-03, a baseline HAE attack rate of 1 attack per 4 weeks was requested. The approved indication does however not

include any restrictions on disease severity. Taking the mechanism of action into account, it was considered by CHMP that the kallikrein-kinin system probably is involved in angioedema formation also in HAE of other types, supporting a broad HAE indication despite the fact that only patients with HAE Type I and II were included in Study DX-2930-03. Likewise, in the present study, only subjects with HAE Type 1 and Type 2 were studied.
Overall, the eligibility criteria are considered to reflect the target population.

The study comprised of two 26-weeks long treatment periods, Treatment Period A and Treatment Period B. During Treatment Period A, dosing was age based (6 to <12 years of age: lanadelumab 150 mg q2wks; 2 to <6 years of age: 150 mg q4wks). In Treatment Period B, subjects 6 to <12 years of age could switch to150 mg q4wks if they had been well controlled (e.g., attack-free) for 26 weeks.

The main objectives of the study were safety and pharmacokinetics. There was thus no primary efficacy endpoint in the study. The main efficacy outcome, assessed as a secondary endpoint, change in number of investigator-confirmed HAE attacks for the Overall Treatment period, is considered clinically relevant and was also accepted as the primary endpoint in Study DX-2930-03.

The sample size was driven by feasibility considerations as enrolment of paediatric subjects 2 to <12 years old was expected to be difficult. At least 20 paediatric subjects (2 to <12 years of age) with at least 5 subjects in each age group of 2 to <9 years of age and 9 to <12 years of age were planned for enrolment to ensure that a minimum of 15 subjects complete 52 weeks of treatment on the study.

Due to the limited population and the lack of comparator, only descriptive statistics applied.

Given the rarity of the disease in general and in the paediatric population in particular, study design and conduct are considered acceptable.

Efficacy data and additional analyses

Study Population

The planned sample size was reached. In total, 24 subjects were screened, and 21 subjects enrolled in the study (age cohort 2-<6 years: n=4, age cohort 6-<12 years: n=17).

Of the 21 subjects treated in the study, 20 subjects completed study treatment (Treatment Period A and B; 52 Weeks). The remaining subject discontinued the study prematurely at day 32 due to withdrawal by the parent/guardian, leaving the 2-<6-year age cohort with only 3 subjects from Week 5.

The mean age in the 2-<6-year cohort was 4.45 years and in the 6-<12-year cohort 8.68 years. The youngest subject enrolled was 3.5 years old and the lowest weight was 15.8 kg. The older age cohort is considered acceptable in age distribution with a substantial representation of subjects in the lower part of the age interval. Albeit formally fulfilling the planned sample size with 5 subjects in the age group of 2 to <9 years of age, the representation of the 2-<6-year cohort is very scarce and non-existing below the age of 3.5 years.
Both sexes were represented in the study. Participants were recruited from EU and North America (US, Canada). Of 21 subjects in the study, 6 subjects (28%) were from the EU. In Study DX-2930-03, a comparable fraction (21%) of the subjects were from Europe.
The mean number of historical HAE attacks was similar in the two age cohorts (e.g., 17 HAE attacks during the last 12 months on the younger age cohort versus 15.2 in the older age cohort) but markedly lower than in study DX-2930-03 (36 HAE attacks during the last 12 months). The same pattern was seen during the run-in period (1.86, 1.84 and 3.48 attacks/month for younger and older age cohort in Study SHP643-301, and

DX-2930-03, respectively). A difference in attack rate between that paediatric and adult studies was anticipated, as the attack rate often increases in children with HAE reaching puberty.
Altogether, the study populations in studies DX-2930-03 and SHP643-301 are considered comparable with the exception of age.

In both the 2-<6 and 6-<12 age cohorts, there were subjects with over 50 HAE attacks during the last 12 months before the study, supporting the need for a prophylactic treatment also in younger children.

Seven subjects switched from q2wks to q4wks dosing during Treatment Period B. In addition, one subject (2-<6-years of age) switched dosing from q4wks to q2wks in Treatment Period B due to recurrent attacks at the q4wks dose. At the q4w dosing (210 days), this subject experienced a HAE attack rate of 0.7 attacks/month, decreasing to 0.2 attacks/month after the switch (152 days).
In the approved posology for adults and adolescents, there is a wording reflecting the possibility of reducing the dose in asymptomatic subjects. A similar wording is proposed for the paediatric population. This measure to avoid unnecessarily high dosing is appreciated. No subject switching to a lower dose in Treatment Period B returned to the higher dose due to recurrence of symptoms.

Results

The main efficacy outcome was Number of Investigator-confirmed HAE Attacks results for the Overall Treatment Period (Day 0 through Day 364) as expressed as mean number of HAE attacks/month (HAE attack rate). Baseline HAE attack rate was established during the run-in period.
No comparative statistical analyses were planned or performed in Study SHP643-301. There was however a marked numerical decrease in HAE attack rate from 1.84 attacks/month at baseline to 0.08 through Day 364 (change from baseline: 95%), supporting a positive and clinically relevant effect on the rate of HAE attacks in the overall study population.

Given the very low number of subjects in the younger age cohort (n=4 of which one discontinued the study at Day 32 and one switched to q2W dosing day 211), no conclusions could be drawn from this population. Data from Treatment Period A does however suggest a similar treatment effect in both age cohorts (2-<6: 1.72 to 0.15 attacks/month [95% reduction]; 6-<12: 1.84 to 0.08 attacks/month [93% reduction]). A subgroup analysis per age group for the Overall Treatment period also indicate a positive effect in the younger age cohort (1.86 to 0.18 attacks/month [94% reduction]). This data should however be interpreted with very large caution.

The results from the main efficacy outcome are supported by other secondary efficacy endpoints, for example attack-free subjects. During the Overall Treatment period, 16/21 (76%) of the subjects were attack-free compared to none during the baseline observation period. Of note, the baseline observation period was up to 84 days long compared to the 364 days of the Overall Treatment period, further emphasising a positive effect on HAE Attack rate. There was a numerically higher percentage of attack-free subjects in the lanadelumab 150 mg q4w versus the 150 mg q2w cohort (91% and 72%, respectively). This is anticipated since subjects treated with lanadelumab 150 mg q2w through Day 182 were allowed to switch to the 150 mg q4w posology if attack-free.

Altogether, the limited efficacy data from Study SHP643-301 is fully in line with the data from study DX-2930-03 and its extension study DX-2930-04, and in support of a consistent and clinically relevant positive effect of lanadelumab in children 6-12 years of age.

A similar positive treatment effect was seen also in the age cohort 2-<6 years; however, the data should be interpreted with caution due to this very limited population (n=3 after treatment week 5). Additional data in particular from the PD popPK analysis would support extrapolation in this young age group. (see below).

Additional aspects related to extrapolation of data

Due to the rareness of HAE in pre-pubertal children, approval of Takhzyro in the paediatric population is based on clinical data from Study SHP643-301 in combination with extrapolation of data from the pivotal adult and adolescent study DX-2930-03.

There are no indications that the pathogenesis of HAE is different in the paediatric versus the adult and adolescent populations. This is supported by the pharmacodynamic marker cHMWK as detailed in the discussion on clinical pharmacology (section 2.6.3.). Furthermore, as discussed above, the study populations in studies DX-2930-03 and SHP643-301 are considered comparable with the exception of age.

The median age for first symptom onset reported from large studies is generally greater than 6 years of age. Overall, 21 subjects received at least 1 dose of lanadelumab in Study SHP643-301 and were included in the safety and PK datasets, however most subjects (n=17) were in the 6 to <12 years age group. Given that there are no known differences in the clinical presentation (other than a lower frequency and severity of attacks) in children <12 years or differences in the underlying pathophysiology of HAE between adult and paediatric subjects with HAE, efficacy in the paediatric population 2 to <12 years was supported by PK exposure matching and extrapolation of efficacy from adolescents (12 to <18 years) and adults (≥18 years). Population PK modelling served as the primary basis of estimating lanadelumab PK parameters (i.e., the primary endpoint) for Study SHP643-301.

Dosing recommendations

The fixed age-based dosing regimens in Study SHP643-301 were selected based on population PK simulations using a model generated from adult data and exposure-response analysis. The results show that children 2-5 years old have a low Cmin with the posology initially proposed by the MAH, based on age-bands, compared to the target exposure in adults. Further, concluding that Cavg is the driving parameter for efficacy and that Cmin has no impact on efficacy has not been convincingly demonstrated. Therefore, based on the totality of evidence submitted, it was concluded that Cmin must also be considered when determining the appropriate posology. Further information is provided in discussion on clinical pharmacology (see section 2.6.3).

Given that weight is a more relevant factor to exposure than age (see section 2.6.3), a posology based on weight bands has therefore been introduced in subjects 2 - <12 years of age in section 4.2 of SmPC. Taking the PK parameters Cmax, Cmin and Cavg into account, an acceptable posology could be identified for all weight bands except for patients weighing 10 - <20 kg. The posology proposed, 150 mg q4w, is expected to yield a too low Cmin in a majority of children weighing 10- <20 kg compared to adults given 300 mg Q2W, whereas Cmax is expected to exceed adult Cmax with approximately 38% (geometric mean). This is similar to the Cmax accepted for adolescents given 300 mg q4w at Takhzyro marketing authorisation. With a dosing of 75 ug q2w, this population is expected to have similar Cmax, Cavg and Cmin as adults on the approved dose. However, there is no prefilled syringe available for administration of 75 mg. Finally, 150 mg q3w in children weighing 10 - <20 kg would yield an acceptable Cmin and Cavg but a Cmax approximately 55% higher than in adults (geometric mean) with 42% of the population expected to exceed the 95th percentile for adults. There are no signals indicating any safety issues associated with this. Nevertheless, it is considered more prudent to start with a more conservative dosing, thereby also avoiding an unnecessary high dosing frequency in the smallest children. Therefore, a starting dose of 150 mg Q4W for children weighing 10 - <20

kg, with a possibility to switch the dosing interval to 150 mg Q3W if necessary due to insufficient attack control, is considered an acceptable dosing strategy as detailed in section 4.2 of SmPC.

A weight band-based dosing was discussed also for adult and adolescent subjects. However, in order to avoid the trouble and potential risk for medicinal error with changing an established posology, keeping the age-based posology in adults and adolescents is accepted. Further, a wording informing on the handling of dosing when switching from paediatric to adult/adolescent posology and a notion that the "paediatric dosing" may also be considered as starting dose in adults and adolescents with a body weight < 40 kg have been introduced in section 4.2 of the SmPC. Further, recommendations for missed doses recommendations have been added in section 4.2 of SmPC.

Based on this, extrapolation of efficacy from the adult and adolescent populations in Study DX-2930-03 to support the limited clinical data from Study SHP643-301 is considered adequate as the MAH has provided an acceptable posology for children 2 to < 12 years of age rendering similar levels of drug exposures as for the approved populations.

2.6.7. Conclusions on the clinical efficacy

Hereditary angioedema (HAE) is a rare genetic disease, which is normally even more rare and milder in children. Nevertheless, pre-treatment data from Study SHP643-301 supports the need for a prophylactic treatment also in younger children.

With only 21 subjects enrolled in the study, of which 17 were 6-<12 years of age and four 3.5-<6 years of age, Study SHP643-301 is considered to mainly provide supportive data.

The limited efficacy data from Study SHP643-301 is in support of a positive effect of lanadelumab in children 6-12 years of age. A similar positive treatment effect was seen also in the age cohort 2-<6 years; however, no firm conclusions can be drawn from this very limited population (n=3 after treatment week 5).

In view of the scarcity of paediatric data, the rarity of the disease and the common pathogenesis of HAE between children and adults/adolescents, extrapolation of efficacy from the adult and adolescent populations in Study DX-2930-03 to support the limited clinical data from Study SHP643-301 is considered adequate.

2.6.8. Clinical safety

Study SHP643-301, which was a single arm study, is the only study within the clinical development program to include paediatric subjects (2 to <12 years). The safety profile of lanadelumab was previously established in adult and adolescents (12 to <18 years) from the pivotal Phase 3 study (Study DX-2930-03) and the OLE study (Study DX-2930-04) (EMEA/H/C/4806).

2.6.8.1. Patient exposure

After the 26-week Treatment Period A, subjects were allowed to change dose regimen. In Treatment Period B, 7 subjects 6 to <12 years switched to the q4wks dose regimen, and 1 subject (6 to 12 years of age) switched to the q2wks dose regimen.

The overall treatment exposure is summarised in Table 17.

Table 17: Overall Study Drug Exposure by Treatment Group (Safety set) (Truncated by Assessor)

Parameter Statistic	Lanadelumab 150 mg q4wks	Lanadelumab 150 mg q2wks	Total
Overall Treatment Period	**N=11**	**N=18**	**N=21**
Total dose (mg) received[a]			
n	11	18	21
Mean (SD)	1118.2 (529.75)	3191.7 (975.92)	3321.4 (940.69)
Median	1050.0	3975.0	3300.0
Min, max	300, 2100	1950, 4050	300, 4050
Time on study (months)[b]			
n	11	18	21
Mean (SD)	6.58 (3.476)	10.48 (2.991)	12.43 (2.598)
Median	6.04	13.00	13.04
Min, max	1.1, 13.0	6.0, 13.3	1.1, 13.3
Duration of time on study[c] – n (%)			
<1 month	0	0	0
1-<3 months	1 (9.1)	0	1 (4.8)
3-<6 months	4 (36.4)	0	0
6-≤13 months	6 (54.5)	9 (50.0)	6 (28.6)
>13 months	0	9 (50.0)	14 (66.7)
Total patient-year (years)	5.55	14.47	20.02

Approximately half of the doses (46.3%) were administered by study staff in the clinic while approximately the other half of the doses were administered by a parent/caregiver either at home (26.6%) or in the clinic (20.9%).

2.6.8.2. Adverse events

A summary of TEAEs during the Overall Treatment period (i.e., Treatment Period A, Treatment Period B, and the follow-up period combined), excluding HAE attack reported events, is presented in Table 18 for the safety set.

Table 18: Overall Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) by Treatment Group (Safety Set)

	Lanadelumab 150 mg					
	q4wks (N=11)		q2wks (N=18)		Total (N=21)	
Category	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Total patient-years (years)					21.35	
Any TEAE	6 (54.5)	43	15 (83.3)	167	17 (81.0)	210
Any related TEAE	3 (27.3)	22	6 (33.3)	99	7 (33.3)	121
Any serious TEAE	0	0	0	0	0	0
Any related serious TEAE	0	0	0	0	0	0
Any severe TEAE	1 (9.1)	6	1 (5.6)	14	1 (4.8)	20
Any related severe TEAE	1 (9.1)	6	1 (5.6)	14	1 (4.8)	20
Any investigator-reported AESI	0	0	0	0	0	0
Deaths due to TEAE	0	0	0	0	0	0
Hospitalizations due to TEAE	0	0	0	0	0	0
Study discontinuation due to TEAE	0	0	0	0	0	0

AE=adverse event; AESI=adverse event of special interest; HAE=hereditary angioedema; m=total number of events; n=number of subjects experiencing the event; q2wks=every 2 weeks; q4wks=every 4 weeks; TEAE=treatment-emergent adverse event.
Notes: Percentages were based on all subjects in the safety set.
Subjects are presented based on the actual treatment regimen received; due to dose modifications, some subjects were treated with both dosing regimens and were counted in each treatment regimen.
Subjects were counted once per category within each column.
Related TEAEs were TEAEs classified as related to lanadelumab by the investigator.
Severe TEAEs were TEAEs classified as severe (grade 3) or life-threatening (grade 4) by the investigator using Division of Microbiology and Infectious Disease criteria.
Hereditary angioedema attack reported AEs included the subset of AEs identified in the electronic data capture as reported HAE attacks.
Adverse events of special interest were determined by the investigator as hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events).
Total patient-years was equal to the sum of (the end date of the period – first date of the period + 1)/365.25 based on the actual treatment received.

Table 19: Treatment-Emergent Adverse Events (Excluding HAE Attack Reported Events) Reported by ≥2 Subjects Overall by System Organ Class, Preferred Term and Treatment Group (Safety Set)

	Lanadelumab 150 mg					
Category	q4wks (N=11)		q2wks (N=18)		Total (N=21)	
System Organ Class Preferred Term	n (%)	m	n (%)	m	n (%)	m / Rate
Overall Treatment Period						
Total patient-years (years)					20.02	
Any TEAE	6 (54.5)	42	15 (83.3)	167	17 (81.0)	209 / 10.44
Eye disorders	0	0	2 (11.1)	2	2 (9.5)	2 / 0.10
Gastrointestinal disorders	1 (9.1)	1	5 (27.8)	7	5 (23.8)	8 / 0.40
Abdominal pain	1 (9.1)	1	2 (11.1)	3	2 (9.5)	4 / 0.20
General disorders and administration site conditions	3 (27.3)	23	7 (38.9)	104	8 (38.1)	127 / 6.34
Injection site pain	2 (18.2)	12	6 (33.3)	76	6 (28.6)	88 / 4.40
Injection site erythema	2 (18.2)	8	2 (11.1)	21	3 (14.3)	29 / 1.45
Pyrexia	0	0	2 (11.1)	2	2 (9.5)	2 / 0.10
Infections and infestations	3 (27.3)	4	10 (55.6)	14	11 (52.4)	18 / 0.90
Nasopharyngitis	1 (9.1)	1	2 (11.1)	2	2 (9.5)	3 / 0.15
Upper respiratory tract infection	0	0	2 (11.1)	2	2 (9.5)	2 / 0.10
Injury, poisoning and procedural complications	3 (27.3)	6	5 (27.8)	18	6 (28.6)	24 / 1.20
Skin abrasion	1 (9.1)	3	3 (16.7)	13	3 (14.3)	16 / 0.80
Joint injury	2 (18.2)	2	0	0	2 (9.5)	2 / 0.10
Musculoskeletal and connective tissue disorders	0	0	3 (16.7)	3	3 (14.3)	3 / 0.15
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	3 (16.7)	4	3 (14.3)	4 / 0.20
Skin papilloma	0	0	3 (16.7)	4	3 (14.3)	4 / 0.20
Nervous system disorders	1 (9.1)	1	2 (11.1)	3	3 (14.3)	4 / 0.20
Headache	1 (9.1)	1	2 (11.1)	3	3 (14.3)	4 / 0.20
Respiratory, thoracic and mediastinal disorders	3 (27.3)	5	3 (16.7)	4	5 (23.8)	9 / 0.45
Nasal congestion	2 (18.2)	2	0	0	2 (9.5)	2 / 0.10
Skin and subcutaneous tissue disorders	1 (9.1)	1	2 (11.1)	4	2 (9.5)	5 / 0.25

AE=adverse event; HAE=hereditary angioedema; m=total number of events; n=number of subjects experiencing the event; q2wks=every 2 weeks; q4wks=every 4 weeks; rate=number of events/total patient-years; TEAE=treatment-emergent adverse event.

Notes: Percentages were based on all subjects in the safety set.
Rates were rounded to 2 decimal places.
Subjects are presented based on the actual treatment regimen received; due to dose modifications, some subjects were treated with both dosing regimens and were counted in each treatment regimen.
Subjects were counted once per system organ class and preferred term.
Hereditary angioedema attack reported AEs included the subset of AEs identified in the electronic data capture as reported HAE attacks.
Total patient-years was equal to the sum of (the end date of the period – first date of the period + 1)/365.25 based on the actual treatment received.

The most frequently reported related non-HAE attack TEAEs overall by PT were injection site pain (6 [28.6%] subjects reported 88 TEAEs with a rate of 4.40), and injection site erythema (3 [14.3%] subjects reported 28 TEAEs with a rate of 1.40).

All other related non-HAE attack TEAEs were reported by 1 (4.8%) subject only; injection site swelling (3 TEAEs with a rate of 0.15), administration site pain, and injection site reaction (1 TEAE each with a rate of 0.05).

One (4.8%) subject (6 to <12 years old) reported a total of 20 severe non-HAE attack TEAEs. Of these events, 16 were considered "life threatening". All 20 severe non-HAE attack TEAEs were within the SOC of general disorders and administration site conditions and were for the PT of injection site erythema. Most of the events recovered within 1 hour and lanadelumab treatment was not interrupted due to these events. No other severe non-HAE attack TEAEs were reported.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

There were no deaths reported during study SHP643-301.

Other Serious Adverse Events

There were no SAEs reported during study SHP643-301.

Discontinuations Resulting from Adverse Events

There were no discontinuations due to TEAEs reported during study SHP643-301.

Other Significant Adverse Events

Hereditary Angioedema Attack Reported Adverse Events

An overall summary of subjects reporting HAE attack TEAEs during study SHP643-301 is reported in Table 20.

Table 20: Overall Treatment-Emergent HAE Attack Reported Adverse Events by Treatment Group (Safety Set)

	Lanadelumab 150 mg					
	q4wks (N=11)		q2wks (N=18)		Total (N=21)	
Category	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Total patient-year (years)					21.35	
Any TEAE	1 (9.1)	5	5 (27.8)	18	5 (23.8)	23
Any related TEAE	0	0	0	0	0	0
Any serious TEAE	0	0	0	0	0	0
Any related serious TEAE	0	0	0	0	0	0
Any severe TEAE	1 (9.1)	2	1 (5.6)	1	1 (4.8)	3
Any related severe TEAE	0	0	0	0	0	0
Deaths due to TEAE	0	0	0	0	0	0
Hospitalizations due to TEAE	0	0	0	0	0	0
Study discontinuation due to TEAE	0	0	0	0	0	0

AE=adverse event; AESI=adverse event of special interest; HAE=hereditary angioedema; m=total number of events; n=number of subjects experiencing the event; q2wks=every 2 weeks; q4wks=every 4 weeks TEAE=treatment-emergent adverse event
Notes: Percentages were based on all subjects in the safety set.
Subjects are presented based on the actual treatment regimen received; due to dose modifications, some subjects were treated with both dosing regimens and were counted in each treatment regimen.
Subjects were counted once per category within each column.
Related TEAEs were TEAEs classified as related to lanadelumab by the investigator.
Severe TEAEs were TEAEs classified as severe (grade 3) or life-threatening (grade 4) by the investigator using Division of Microbiology and Infectious Disease criteria.
Hereditary angioedema attack reported AEs included the subset of AEs identified in the electronic data capture as reported HAE attacks.
Adverse events of special interest were determined by the investigator as hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events).
Total patient-years was equal to the sum of (the end date of the period – first date of the period + 1)/365.25 based on the actual treatment received.

Hypersensitivity Reactions

Overall, 4 (19.0%) subjects reported a total of 7 non-HAE attack TEAEs of SMQ-defined hypersensitivity, including one subject who developed antidrug antibodies (ADAs) during the study. The most frequently reported SOC in this category was skin and subcutaneous tissue disorders with 2 (9.5%) subjects reporting 5 events, and the most frequently reported PT was erythema with 1 (4.8%) subject reporting 2 events. None of the 7 non-HAE attack TEAEs of SMQ-defined hypersensitivity were considered related to lanadelumab, and none of the events were severe in intensity.

The subject who developed ADAs and had an SMQ-defined hypersensitivity reaction experienced 1 non-HAE attack TEAE of eosinophil count increased, which was mild in severity. The event did not occur at the time the subject tested ADA positive and resolved without any action taken.

Bleeding Events

Overall, 3 (14.3%) subjects reported a total of 4 non-HAE attack TEAEs of SMQ-defined bleeding events. The most frequently reported SOC in this category was vascular disorders with 1 (4.8%) subject reporting 2 events; both events were for the PT of hematoma. All other non-HAE attack TEAEs of SMQ-defined bleeding events were reported once by 1 (4.8%) subject overall.

None of the 4 non-HAE attack TEAEs of SMQ-defined bleeding events were considered related to lanadelumab, and none of the events were severe in intensity.

Hypercoagulability Events

No AESIs of hypercoagulation were reported by the investigators, and no non-HAE attack TEAEs of SMQ-defined hypercoagulation were recorded in Study SHP643-301.

Injection Site Reactions

Overall, 7 (33.3%) subjects reported a total of 123 TEAEs of ISRs; 121 of which were considered related to lanadelumab, and 20 were considered related and severe in 1 subject.

All 123 ISR TEAEs reported were within the SOC of general disorders and administration site conditions. The most frequently reported ISR TEAEs overall by PT were injection site pain (6 [28.6%] subjects reported 88 TEAEs with a rate of 4.40), and injection site erythema (3 [14.3%] subjects reported 29 TEAEs with a rate of 1.45).

2.6.8.4. Supportive Safety Findings

The safety profile of lanadelumab was previously established in adult and adolescents (12 to <18 years) from the pivotal Phase 3 study (Study DX-2930-03) and the OLE study (Study DX-2930-04). Overall, the occurrence of commonly reported AEs in paediatric subjects in Study SHP643-301 was generally consistent with that previously reported in adults and adolescents from Studies DX-2930-03 and DX-2930-04.

The most frequently reported TEAEs (excluding HAE attack reported events) by system organ class (SOC) in lanadelumab-treated subjects in Study DX-2930-03 were general disorders and administration site conditions (54.8%), and infections and infestations (51.2%). The most frequently reported TEAEs by preferred term (PT) were injection site pain (42.9%), viral upper respiratory tract infection (23.8%), headache (20.2%), injection site erythema (9.5%), injection site bruising (7.1%), and dizziness (6.0%).

In Study DX-2930-04, TEAEs (excluding HAE attack reported events) were most frequently reported within the SOCs of infections and infestations (79.7%), and general disorders and administration site conditions (61.8%). The most frequently reported TEAEs by PT were injection site pain (47.2%), viral upper respiratory tract infection (42.0%), upper respiratory tract infection (25.9%), and headache (24.5%).

Overall, the occurrence of injection site reactions (ISRs) in paediatric subjects in StudySHP643-301 was generally consistent with the occurrence reported in adults and adolescents in Studies DX-2930-03 and DX-2930-04.

In Study DX-2930-03, 84 lanadelumab-treated subjects received 2118 injections and had 398 ISRs (18.8%). There were no serious or severe ISRs reported in lanadelumab-treated subjects, and most of the ISRs were mild in severity. The most frequent ISRs reported by PT were injection site pain (42.9%), injection site erythema (9.5%), and injection site bruising (7.1%). The majority of ISRs were considered related to lanadelumab treatment and resolved within 30 minutes.

During the treatment period of Study DX-2930-04, 117 (55.2%) subjects had a total of 2287 ISRs. These ISRs occurred across a collective 11899 doses. The most frequent ISRs reported by subjects overall by PT during the treatment period were injection site pain (47.2%), injection site erythema (17.0%), injection site bruising (12.3%), and injection site swelling (8.0%). None of the ISRs were serious or severe, and most were

mild in severity. The majority of ISRs were related to lanadelumab treatment and resolved within a day (70.2% resolved within an hour)

2.6.8.5. Laboratory findings

According to the MAH, the majority of subjects had normal clinical laboratory values throughout study SHP643-301. Overall, no clinically meaningful changes from baseline were observed for either treatment group for any of the laboratory parameters. This is further reviewed in the Discussion on Clinical Safety.

Two subjects were reported with clinically significant abnormal laboratory results. One subject who switched from the q2wks to q4wks treatment regimen experienced 2 postbaseline clinically significant abnormal chemistry values, both of which were during the q2wks treatment regimen at Visit 16 (Day 112); the subject had a low chloride value and a high sodium value on this day. In addition, one subject in the q2wks group had 1 event of eosinophil count increased, which was considered clinically significant at Visit 1; this event was reported as a TEAE and was considered mild in severity.

2.6.8.6. In vitro biomarker test for patient selection for safety

N/A

2.6.8.7. Safety in special populations

The safety database in the paediatric population consists of 21 subjects aged 3.5 to 12 years. No subgroup analyses of safety in different ages, gender or race are considered meaningful.

No new safety data for adolescents, adults or elderly were provided in the current procedure.

2.6.8.8. Immunological events

The methodology for measuring ADAs (ie, anti-lanadelumab antibodies) is discussed in detail in the Clinical Pharmacology section.

At baseline, no subjects in either treatment group were positive for ADAs.

During the Overall Treatment period, 3 (15.0%) subjects were ADA positive; all of which were in the q2wks group and were 6 to <12 years of age. Of these, one (33.3%) subject had neutralizing antibodies on one occasion. For further details, please refer to Clinical Pharmacology section/Pharmacokinetic AR.

The subject with neutralizing antibodies experienced one non-HAE attack TEAE of SMQ-defined hypersensitivity and 2 non-HAE attack TEAEs of injection site reactions. All three of these events resolved, and none of the events occurred at the time the subject tested ADA positive.

The formation of ADAs and neutralizing antibodies had no impact on clinical outcomes, PK, PD, or the safety of lanadelumab over the 52-week treatment period. The three subjects who were ADA positive were attack-free during the study, had similar lanadelumab concentrations and cleaved high molecular weight kininogen levels to subjects who were ADA negative, and had no differences in hypersensitivity related events or TEAEs from ADA negative subjects.

2.6.8.9. Safety related to drug-drug interactions and other interactions

No specific interactions are anticipated in the paediatric population.

2.6.8.10. Discontinuation due to adverse events

There were no TEAEs leading to discontinuation reported in the study.

2.6.8.11. Post marketing experience

Worldwide Marketing Experience

Patient exposure is roughly estimated on the basis of worldwide sales figures and shipment data. It is estimated that 6,345 patient-year exposures to lanadelumab have occurred cumulatively in the post-marketing setting since first market launch (2018) through 22 Feb 2022.

Post-marketing Safety

Overview of Case Reporting

Overall, post-marketing safety data are consistent with the safety profile observed in clinical trials of lanadelumab. No new safety issues have been identified in the post-marketing environment.

Adverse drug reactions from post-marketing sources were most frequently reported in the SOCs of congenital, familial and genetic disorders; general disorders and administration site conditions; infections and infestations; and injury, poisoning and procedural complications.

Similar patterns of reporting were observed for both healthcare professional and non-healthcare (ie, consumer) reports.

As with all sponsor-marketed products, the safety profile of lanadelumab is closely monitored and evaluated on a continual basis, as per the Risk Management Plan.

Overview of Cases in Adults and Adolescents

A cumulative review of cases reported from post-marketing sources up to and including 22 Feb 2022, identified a total of 2111 cases (3740 events) reported in adults and adolescents aged >12 years.

Of these, 1540 events were from solicited non-interventional sources (all of which were serious), and 2200 events were spontaneous (including worldwide competent authorities and scientific literature). Of the 2200 spontaneous events, 247 events were serious, and 1953 events were nonserious.

Among the serious cases, the most commonly reported events, in descending order of frequency, were HAE, hospitalization, and pneumonia. Among the nonserious cases, the most commonly reported events, in descending order of frequency were HAE, product dose omission issue, and inappropriate schedule of product administration. These events are primarily consistent with the clinical presentation of the underlying HAE, and the TEAEs observed during the clinical development program of lanadelumab.

2.6.9. Discussion on clinical safety

The safety database for the paediatric population is very limited and comprises of a total exposure of 20 patient-years (PY); 5.6 PY with the q4W dosing and 14.5 PY with the q2W dosing.

In total, 81% of the study population reported at least on TEAE (54% with the q4w regimen and 83% with the q2w regimen). The differences between the groups could reflect the discrepancy in exposure between the regimens and/or that the risk of injection site reactions is higher with more frequent administration.
In Study DX-2930-03, 91% of the subjects reported at least one TEAE.

The most frequently reported TEAEs (excluding HAE attack reported events) by SOC in lanadelumab-treated subjects in Study DX-2930-03 were "general disorders and administration site conditions" (55% of the subjects), and "infections and infestations" (51%). In Study SHP643-301, the corresponding frequencies were 38% and 52% respectively for "general disorders and administration site conditions" and "infections and infestations". However, more events were reported in the SOC "general disorders and administration site conditions" (6.34 events per PY), mainly representing injection site reactions.

One single subject reported a total of 20 severe non-HAE attack TEAEs, all within the SOC of "general disorders and administration site conditions" and for the PT of injection site erythema. Of these events, 16 were considered "life threatening". Nevertheless, this subject completed study treatment. The MAH has clarified that according to the Division of Microbiology and Infectious Disease (DMID) Paediatric Toxicity table presented in appendix to protocol for SHP643-301, a local reaction larger than 50 mm is per definition labelled as "grade 4", i.e., "life threatening".

There were no deaths, discontinuations due to adverse events or serious adverse events (SAEs) reported during the study. No TEAEs of hypercoagulation were reported.

It is agreed that there were few clinically relevant changes in laboratory values during the study. However, many of the subjects had very similar laboratory aberrations both at screening and during the study. These included low creatinine, low bicarbonate, high magnesium, and high serum albumin. Low creatinine may reflect low muscle volume in a paediatric population with chronical illness, but the general pattern of laboratory chemical aberrations is not fully understood. Notwithstanding, since the laboratory aberrations where often seen at screening and/or before treatment Day 0, and since there were seemingly no trends in laboratory values over time during treatment, this is not further pursued.
Moreover, the flagging for clinical significance made by the Investigators seems somewhat arbitrary. For one subject, sodium 154 mEq/L (ref 133-145 mEq/L) was flagged as clinically significant at one visit, whereas sodium 176, 173, and 156 mEq/L at other visits in the same subject were not. Furthermore, no low bicarbonate value in any subject was flagged as clinically relevant, even though levels of 9-15 mEq/L were reported in several subjects (ref 20-28 mEq/L). These low levels of serum bicarbonate are normally considered relevant in clinical praxis and medical action would normally be expected. The MAH has clarified that abnormal laboratory values, which were unexpected or not explained by the subject's clinical condition, may have, at the discretion of the investigator or sponsor, been repeated as soon as possible until confirmed, explained, or resolved. Therefore, abnormal laboratory values detected in the study were not always reported. For example, the highly abnormal laboratory sodium 176 mEq/L and bicarbonate 9 mEq/L were repeated and found erroneous.

Three subjects (14%) reported new-onset transient anti-drug antibodies (ADA), all but one with non-neutralising antibodies at a very low titre (20). For comparison, in Study DX-2930-03, the overall incidence of ADA in lanadelumab treated subjects was 10 of 84 (11.9%).

One subject in Study SHP643-301 had neutralising ADA at Visit 20 and non-neutralising at the next measurement (Visit 26). This subjects also reported one hypersensitivity TEAE and two injections site reactions, however not coinciding with the ADA positivity. The hypersensitivity event (eosinophils increased) was reported at Day 0 and all events resolved without any action taken. It is therefore agreed with the MAH that these events are not causally associated with positive ADA.
Two subjects in Study DX-2930-03 (lanadelumab 150 mg q4wks arm) tested positive for low titre antibodies classified as neutralising.
It is considered reassuring that all three subjects with transient ADA-positivity in Study DX-2930-03 were attack-free during the study, had similar lanadelumab concentrations and cleaved high molecular weight kininogen levels as subjects who were ADA negative, and had no differences in hypersensitivity related events or TEAEs from ADA negative subjects.

No new and unexpected safety finding were identified in Study SHP643-301. Overall, the safety profile in paediatric subjects in Study SHP643-301 was generally consistent with that previously reported in adults and adolescents in the pivotal Phase 3 study and the OLE study (Studies DX-2930-03 and DX-2930-04). The data have been reflected in section 4.8 of SmPC.

As pointed out earlier, the safety data base for the lanadelumab treated paediatric population is very scarce, especially in children below the age of six years. As discussed for efficacy, extrapolation from the adult and adolescent populations are warranted.
The MAH refers to the nonclinical safety studies evaluating SC administration of lanadelumab for up to 6 months in cynomolgus monkeys and considers this to support use in the paediatric patient population aged ≥ 2 to <12 years. Please refer to non-clinical discussion section for further details.

Extrapolation of safety from adults and adolescents to the paediatric population

The MAH provided additional argumentation for extrapolation of safety data from adults and adolescents to young children, based on e.g., the specificity of the antibody, data from subjects with an inborn genetic prekallikrein deficiency and additional non-clinical data.
In summary, lanadelumab did not inhibit a panel of 20 different serine proteases, a class of proteases that includes pKal and share catalytic mechanism and key active site amino acids, at a dose three times higher than Cmax in adults. Furthermore, the binding of the antibody only to epitopes present in the active form of the enzyme (pKal) and not to prekallikrein, allowing regulation of pKal activity to generate a basal level of bradykinin prior to reversible binding by lanadelumab. It is agreed that this diminishes the risk of off-target effects of relevance for juvenile development.

The MAH also presented data from a publication describing 111 cases of prekallikrein deficiency from 89 families (Barco et al, 2015). Most cases of prekallikrein deficiency are not identified until adulthood and are incidental to testing for a different condition, for example prolonged APTT (activated partial thromboplastin time) without bleedings discovered during work-up prior to routine surgery. In the article, which represents the largest study performed on subjects with severe prekallikrein deficiency, there were no indication of any impact on juvenile development in this cohort which is reassuring.

Finally, the MAH referred to the results from the non-clinical ePPND study on pre- and postnatal developmental toxicity in cynomolgus monkeys which showed potential exposure to lanadelumab through placental transfer in utero and through breast milk. There was no adverse maternal or infant findings in the study. This is considered to support the safety of lanadelumab in young children. Further details can be found in the non-clinical discussion section.
Altogether, it is agreed that there is no indication that inhibition of kallikrein is associated with specific safety

concerns in young children compared to adults and adolescents during long-term treatment. However, there is a need to monitor the safety in children post-approval through routine pharmacovigilance activities considering the very limited dataset.

Furthermore, there were no signals indicating any safety issue associated with the various dosing regimen including the posology of 150 mg every 3 weeks for children weighing 10 to less than 20 kg for which the Cmax would be approximately 55% higher than in adults (geometric mean) with 42% of the population expected to exceed the 95th percentile for adults in the limited clinical data.

In light of the above, it is considered acceptable to monitor long-term safety in children on lanadelumab treatment via routine pharmacovigilance.

2.6.10. Conclusions on the clinical safety

No new and unexpected safety finding were identified in Study SHP643-301. Overall, the safety profile in paediatric subjects in Study SHP643-301 was generally consistent with that previously reported in adults and adolescents in the pivotal Phase 3 study and the OLE study (Studies DX-2930-03 and DX-2930-04).

As the safety data base for the lanadelumab treated paediatric population is very scarce, especially in children below the age of six years, there is a need to continue monitoring of safety post approval to characterise the safety profile in the paediatric population in particular the youngest age group through routine pharmacovigilance activities (i.e., adverse reactions reporting and signal detection).

2.7. Risk Management Plan

2.7.1. Safety concerns

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

2.7.2. Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
NA	NA	NA	NA	NA
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				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
NA		NA	NA	NA

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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:** None.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 3.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Takhzyro, EMEA/H/C/004806/II/0012/G. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HAE is a rare hereditary disease usually beginning between 5 and 11 years of age (Farkas 2010) with diagnosis a couple of year later. HAE is thus even rarer in prepubertal children. Nevertheless, the historical mean HAE attack rate was 16 attacks during the 12 months before treatment in the paediatric study presented in this application, supporting an unmet medical need for routine prophylaxis also in children below the age of 6 years. Furthermore, albeit HAE attacks often are milder in children, the medical and social consequences of frequent HAE attacks in children and adolescents are large.

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, leading to a negative impact on health (e.g., failure to thrive in young children with nausea due to GI-attacks) and social situation (e.g., social stigmata, time away from school, etc). In addition, laryngeal attacks may be life-threatening. The HAE attack rate is therefore considered highly clinically relevant.

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

The scope of this procedure is to extend the indication to paediatric patients from 2 years of age.

3.1.2. Available therapies and unmet medical need

There are three categories of treatment available for subjects with hereditary angioedema (HAE): acute treatment of ongoing HAE attacks, pre-procedural prevention, and routine prophylaxis. Pre-procedural prevention is usually a single dose of medication given within 24 hours before a medical, dental, or surgical procedure known to increase the risk of HAE attacks, whereas routine prophylaxis is intended as long-term prevention.

As per January 2023, beside Takhzyro two products, the C1-inhibitor Cinryze and the pKal inhibitor Orladeyo, are indicated for routine prophylaxis of HAE in the EU. For this indication, Cinryze is approved from the age of six years, and Takhzyro and Orladeyo from the age of 12 years.

Furthermore, antifibrinolytic agents (mainly tranexamic acids) are indicated as HAE prophylaxis. In clinical practice, tranexamic acid seems to be mainly used in subjects in which C1-INH replacement therapy is not available or not approved, e.g., children and pregnant women.

3.1.3. Main clinical studies

The main clinical study for extending the indication to the paediatric population was Study SHP643-301.

Study SHP643-301 was an open-label, uncontrolled, multicentre study. The main eligibility criteria were paediatric patients (2 to <12 years) of both sexes with a diagnosis of HAE (Type I or II) and a historical baseline HAE attack rate of ≥1 angioedema attack per 3 months. The baseline HAE attack rate was evaluated during a run-in period of 4-12 weeks.

The main objective of Study SHP643-301 was PK, PD, and safety. Due to the limited population and the lack of comparator in the study, only descriptive statistics applied.

In total, 21 subjects (2-<6 years: 4 subjects; 6-<12 years: 17 subjects) were enrolled in the study. One subject (age cohort 2->6 years) discontinued the study at Day 32 due to withdrawal of consent. All other subjects completed study and study treatment.

The younger age cohort was administered lanadelumab 150 mg every fourth week (q4w) and the older age cohort lanadelumab 150 mg q2w. The Overall Treatment Period was 52 weeks. During the first 26 weeks of the study (Treatment Period A), all subjects were given their assigned age-based dose. During Treatment Period B (weeks 27-52), subjects aged 6-<12 years could switch to the q4w-dosing provided they were attack free for 26 weeks. Seven subjects ages 6-<12 years were administered lanadelumab q4w during at least a part of Treatment Period B. One subject aged 2-<6 years switched from the q4w to the q2w dosing after due to poor efficacy.

3.2. Favourable effects

There was no primary efficacy endpoint in the study. All clinical efficacy outcome endpoints were secondary or tertiary (exploratory) endpoints since safety and PK were the primary objectives of this open-label study.

The main efficacy outcome (normalized number of investigator-confirmed HAE attacks for the Overall Treatment Period) was the primary endpoint in Study DX-2930-03 performed in adults and adolescents, albeit with a shorter observation period (DX-2930-03: 182 days).

<u>Normalized number of investigator-confirmed HAE attacks for the Overall Treatment Period (Day 0 through Day 364)</u>

- Baseline mean (SD) HAE attack rate (attack/month)
    - Lanadelumab 150 mg q4w (n=11): 1.45 (0.79)
    - Lanadelumab 150 mg q2w (n=18): 1.91 (1.63)
    - All subjects (n=21): 1.84 (1.52)
- Overall Treatment Period mean (SD) HAE attack rate (attack/month)
    - Lanadelumab 150 mg q4w (n=11): 0.07 (0.22)

- Lanadelumab 150 mg q2w (n=18): 0.08 (0.16)
- All subjects (n=21): 0.08 (0.16)

Normalized number of investigator-confirmed HAE attacks for Treatment Period A (Day 0 through Day 182) [#]

- Baseline mean (SD) HAE attack rate (attack/month)
  - Lanadelumab 150 mg q4w (n=4): 1.86 (1.03)
  - Lanadelumab 150 mg q2w (n=17): 1.84 (1.64)
  - All subjects (n=21): 1.84 (1.52)
- Treatment Period A mean (SD) HAE attack rate (attack/month)
  - Lanadelumab 150 mg q4w (n=4): 0.15 (0.31)
  - Lanadelumab 150 mg q2w (n=17): 0.08 (0.21)
  - All subjects (n=21): 0.10 (0.22)

[#] Since no switches were allowed during Treatment Period A, this analysis reflects efficacy in each age-cohort during the first 26 weeks.

Achievement of Investigator-confirmed HAE Attack-free during Overall Treatment Period

All 21 subjects experienced at least one HAE attack during the baseline observation period.

- Overall Treatment Period (attack free subjects) [##]
  - lanadelumab 150 mg q4w: 10/11 subjects; 91%
  - lanadelumab 150 mg q2w: 13/18 subjects; 72%

[##] Of note, the baseline observation period was up to 3 months long compared to the 364 days of the Overall Treatment Period. In addition, the difference in the proportion of attack-free subjects between the treatment arms may be explained by the switch of attack-free subjects from the q2w to the q4w dosing.

A reduction of HAE attacks during lanadelumab treatment was reported in study SHP643-301 in all analysis periods. A 95% reduction of HAE attack rate (decrease in HAE attack rate from 1.84 attacks/month at baseline to 0.08) in the total population was reported during the Overall Treatment period (364 days). This is in line with the data from study DX-2930-03 in adults and adolescents, in which HAE attack rate reductions of 84-91% (three dosing levels) were seen during 182 days.

A similar treatment effect was seen in children in the two age cohorts 6-<12 years and 2-<6 years during the first 26 weeks (i.e., Day 0 through Day 182) of Study SHP643-301. A decrease in HAE attack rate from 1.84 attacks/month at baseline to 0.10 attacks/month in the total population was observed. However, the overall number of subjects in the study was low. In total, 21 subjects, of which 17 were 6-<12 years and 4 were 2-<6 years, entered the study. Furthermore, one subject (2 to<6 years of age) discontinued the study prematurely at day 32, leaving the 2-<6-year age cohort with only 3 subjects from Week 5.

3.3. Uncertainties and limitations about favourable effects

The overarching limitation for the clinical efficacy data is the open-label, uncontrolled design of the main study, SHP643-301, in combination with the small sample size (21 patients), in particular in subjects below the age of 6 years (only 4 subjects included). Therefore, only descriptive statistics were applied. This renders the study largely supportive. These data are further supported by PopPK /PD data and extrapolation from data from the pivotal adult and adolescent study DX-2930-03. PopPK data and exposure-response analysis were also supportive of achieving levels of concentration similar to the adolescents and adult population.

For children aged ≥2 years of age, it is not expected that factors other than body weight affect the distribution or elimination of monoclonal antibodies compared to adults.

One limitation to the data is that only 4 children aged <5 years (10-20 kg) were included in the study; however, as the disease is rare, especially in children <6 years of age, it is considered acceptable to extrapolate below 15 kg.

3.4. Unfavourable effects

In total, 81% of the study population reported at least on TEAE (54% with the q4w regimen and 83% with the q2w regimen).

The most frequently reported TEAEs (excluding HAE attack reported events) by SOC in lanadelumab-treated subjects in Study SHP643-301 were "general disorders and administration site conditions" (38% of the subjects), and "infections and infestations" (52%). However, more events were reported in the SOC "general disorders and administration site conditions" (6.34 events per PY versus 0.9 events/PY for "infections and infestations"), mainly representing injection site reactions.

One single subject reported a total of 20 severe non-HAE attack TEAEs, all within the SOC of "general disorders and administration site conditions" and for the PT of injection site erythema. Of these events, 16 were considered "life threatening". Nevertheless, this subject completed study treatment. No other severe non-HAE attack TEAEs were reported.

There were no deaths, discontinuations due to adverse events or serious adverse events (SAEs) reported during the study.

3.5. Uncertainties and limitations about unfavourable effects

The safety database for the paediatric population is very limited and comprises of a total exposure of 20 patient-years (PY); 5.6 PY with the q4W dosing and 14.5 PY with the q2W dosing. The absence of a control group hampers assessment of causal relation of adverse events with lanadelumab.

As for efficacy, the safety of lanadelumab treatment in the paediatric population is supported by the clinical data from Study SHP643-301 together with extrapolation of data from the pivotal adult and adolescent study DX-2930-03.

3.6. Effects Table

The efficacy parameters were secondary end points of the study.

Table 21: Effects Table for Takhzyro for routine prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 2 years and older

Effect	Short Description	Unit	Q4W (n=11)	Q2W (n=18)	Uncertainties/ Strength of evidence	References
Favourable Effects						
HAE attack rate	Median reduction in HAE attack rate during Overall Treatment Period	Attacks/ month	-1.12	-1.20	For all favourable and unfavourable effect, the main uncertainty is the limited sample size	[1]
"-"	Percent reduction in HAE attack rate during Overall Treatment Period	%	98	94		[1]
Attack-free	Percent subjects attack-free during Overall Treatment Period	%	91	72		[1]
Unfavourable Effects						
TEAE	Subjects (n)/events (m) reported TEAE	n (%)/m	6 (54)/ 43	15 (83)/ 167		[1]
SAE	Subjects (n)/events (m) reported SAE	n (%)/m	0	0		[1]
GDASC	Subjects (n)/events (m) reported GDASC	n (%)/m	3 (27)/ 23	7 (39)/ 104		[1]

Abbreviations: GDASC: Adverse event in the SOC *General disorders and administration site condition*; SAE: serious adverse event; TEAE: treatment emergent adverse event; q2w: lanadelumab 150 mg every second week; q4w: lanadelumab 150 mg every fourth week,

Notes:

- [1] Study SHP643-301;
- Overall Treatment Period: Day 0-364;
- *General disorders and administration site condition* was the SOC with most commonly reported adverse events (6.34 events/patient-year during the Overall Treatment period), mainly representing Injection site reactions.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH is applying for a paediatric indication including children from the age of 2 years. The application is based on a small clinical study (SHP643-301) and on extrapolation of efficacy and safety from adolescents and adults (Study DX-2930-03).

Given the rarity of the disease in general and in the paediatric population in particular, study design and conduct are considered acceptable. However, the robustness of Study SHP643-301 is limited by the open-label, uncontrolled study design and the small sample size. Due to these limitations, the study results are seen as supportive together with extrapolation considerations.

The HAE attack rates during the run-in period versus during lanadelumab treatment was the primary endpoint in the pivotal study in the adult and adolescent population, Study DX-2930-03, and the main efficacy outcome in the paediatric study SHP643-301.

A reduction of HAE attacks during lanadelumab treatment was reported in study SHP643-301 in all analysis periods. The magnitude of this treatment effect is considered meaningful from a clinical perspective. The benefit of lanadelumab in the paediatric population is further supported by the relatively large number of attack-free subjects that was observed across all groups during treatment.

A similar treatment effect was seen in children in the two age cohorts 6-<12 years and 2-<6 years during the first 26 weeks of Study SHP643-301. However, the overall number of subjects in the study was low. Therefore, subgroup analyses, especially in the younger age cohort 2-<6 years, need to be interpreted with great caution.
As a result, it is considered that the limited efficacy data from Study SHP643-301 is in support of a positive effect of lanadelumab in the paediatric population.

In view of the scarcity of paediatric data, the rarity of the disease and the common pathogenesis of HAE between children and adults/adolescents, extrapolation of efficacy, based on a population PK model and exposure-response analysis, from the adult and adolescent populations in Study DX-2930-03 to the paediatric population is considered adequate and warranted to support the limited clinical data from Study SHP643-301.

No new and unexpected safety finding were identified in Study SHP643-301. The safety profile in paediatric subjects in Study SHP643-301 was generally consistent with that previously reported in adults and adolescents in the Studies DX-2930-03 and the extension study DX-2930-04. Overall, the safety profile is considered benign and manageable. The majority of treatment emergent adverse events were in the SOC "general disorders and administration site conditions", mainly representing injection site reactions. There were no deaths, discontinuations due to adverse events or serious adverse events reported during the study. As the safety dataset for the paediatric population is very scarce, especially in children below the age of six years, data should be interpreted with great caution.

With regard to extrapolation of safety to the paediatric population, it is acknowledged that there is no indication that inhibition of kallikrein is associated with specific safety issues in young children compared to adults and adolescents during long-term treatment. This is also supported by the non-clinical data, and therefore, extrapolation of safety from the approved populations to children 2- <12 years of age is in principle acceptable.

Overall, the efficacy and safety results from study SHP643-301 were consistent with the results from adolescents and adults population in study DX-2930-03. The population pharmacokinetic (PK) model is generally adequate to capture and simulate the exposure in children 2-<6 years of age for extrapolation.

3.7.2. Balance of benefits and risks

Clinical data from study SHP643-301 together with extrapolation of efficacy data from study DX-2930-03 are considered to support a beneficial treatment effect of Takhzyro on routine prevention of HAE attacks in children 2-<12 years of age as the posology results in similar levels of drug exposure in children and adults. The safety profile in study SHP643-301 was in line with study DX-2930-03 and overall considered benign. Nevertheless, the safety data base for the lanadelumab treated paediatric population is very scarce, especially in children below the age of six years. Extrapolation of safety data from adults to children could in principle be acceptable as the paediatric posology results in similar drug exposure as the adult posology Furthermore, it is not expected that the safety profile differs between children aged 2-<12 years and adolescents and adults.

The MAH has implemented a dosing regimen based on weight-bands for subjects 2-<12 years of age. It is considered acceptable to keep the age-based posology for subjects >12 years of age since a wording informing on the handling of dosing when switching from paediatric to adult/adolescent posology and a notion that the "paediatric dosing" may also be considered as starting dose in adults and adolescents with a body weight <40 kg have been introduced in section 4.2 of the SmPC.

Taking the totality of evidence into account, the data submitted support the approval of Takhzyro for routine prevention of recurrent attacks of hereditary angioedema in children 2 to less than 12 years of age.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of TAKHZYRO is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, TAKHZYRO 150 mg, solution for injection in pre-filled syringe is favourable in the following indication:

TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 years and older.

The CHMP therefore recommends the extension(s) of the marketing authorisation for TAKHZYRO subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

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.

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

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (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.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0214/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

The RMP (version 3.2) is updated in accordance.

A type IB variation (C.I.z) has been submitted to update section 7 of the Package Leaflet (PL) for the 300 mg in 2 ml pre-filled syringe (EU/1/18/1340/004-006) in line with the proposed PL for the 150 mg in 1 ml pre-filled syringe (new strength).