BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761090 s010
Priority or Standard	Priority
Submit Date(s)	August 5, 2022
Received Date(s)	August 5, 2022
PDUFA Goal Date	February 5, 2023
Division/Office	Division of Pulmonology, Allergy, and Critical Care/Office of Immunology and Inflammation
Review Completion Date	February 2, 2023
Established/Proper Name	lanadelumab
(Proposed) Trade Name	Takhzyro
Pharmacologic Class	plasma kallikrein inhibitor (monoclonal antibody)
Code name	SHP643, DX-2930
Applicant	Takeda Pharmaceuticals
Dosage form	Subcutaneous injection
Applicant Proposed Dosing Regimen	Pediatric patients (6 to less than 12 years of age) administer 150 mg every 2 weeks. Dosing every 4 weeks may be considered in some patients. Pediatric patients (2 to less than 6 years) administer 150 mg every 4 weeks.
Applicant Proposed Indication(s)/Population(s)	For prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Unchanged
Recommended Dosing Regimen	Unchanged

Table of Contents

Table of Tables

Table of Figures

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Abbreviations: DEPI: Division of Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; DRISK: Division of Risk Management; OBP: Office of Biotechnology Products; OPDP: Office of Prescription Drug Promotion; OPQ: Office of Pharmaceutical Quality; OSI: Office of Scientific Investigations; OSE: Office of Surveillance and Epidemiology

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BLA	biologics license application
BLQ	below the limit of quantitation
BMI	body mass index
C1-INH	C1-esterase inhibitor
CFR	Code of Federal Regulations
CL/F	apparent clearance
C	plasma concentration
EQ-5D-Y	Euro Quality of Life 5-Dimension
FDA	Food and Drug Administration
GLP	good laboratory practice
HAE	hereditary angioedema
HMWK	high molecular weight kininogen
IND	Investigational New Drug
NDA	new drug application
PedsQL	Pediatric Quality of Life Inventory Generic Core Scale
PD	pharmacodynamics
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SC	subcutaneous
$T_{1/2}$	elimination half-life
TEAE	treatment emergent adverse event
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
V/F	volume of distribution
WR	written request

1. Executive Summary

1.1. Product Introduction

Takeda Pharmaceuticals U.S.A., Inc. submitted an efficacy supplement (S-010) for biologic license application (BLA) 761090 to expand the indication for lanadelumab from 12 years of age down to 2 years of age for prophylaxis to prevent attacks of hereditary angioedema (HAE). Lanadelumab is a fully human monoclonal antibody (IgG1κ) targeting active plasma kallikrein. It was originally approved in 2018 as a prefilled syringe and single-dose vial to be used as a prophylactic agent for HAE in patients aged 12 years and older.

For HAE prophylaxis in patients 12 years of age and older, the approved dosage is 300 mg administered subcutaneously (SC) every 2 weeks. A dosing interval of 300 mg SC every 4 weeks can be given to patients with well controlled disease (attack free for more than 6 months). The Applicant is seeking a new dose of 150 mg administered SC every 2 weeks for children 6 to 11 years of age. For those who are stable and attack free, a reduction in dose frequency to 150 mg every 4 weeks may be considered. For patients 2 to 6 years of age, the Applicant is seeking a new dose of 150 mg administered subcutaneously every 4 weeks. Doses in both age groups are administered in the currently approved presentation as a prefilled syringe but should be administered by a caregiver or health care provider for the newly proposed age groups.

Lanadelumab is currently approved in over 50 countries, including the European Union and the U.S.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for lanadelumab to prevent attacks of HAE in children 2 to < 12 years of age is provided by extrapolation from evidence that supported substantial evidence of effectiveness from the approval of lanadelumab for the same indication in adults and adolescents 12 years of age and older. Based on an overlap in the clinical presentation of both adult and pediatric HAE, consistency in the therapeutic approach, consistency of the lanadelumab mechanism of action, and relevance of the clinical endpoints, efficacy in children 2 to <12 years of age was extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older. Extrapolation is supported by pharmacokinetic (PK) analyses showing similar drug exposure levels for 150 mg administered subcutaneously every 4 weeks for patients 2 to 6 years of age or 150 mg administered subcutaneously every 2 weeks for 6 to <12 years old and a similar pharmacodynamic response. The pharmacodynamics (PD) response was also comparable.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This efficacy supplement for lanadelumab proposes to expand the indication from 12 years of age down to 2 years of age for prophylaxis to prevent attacks hereditary angioedema (HAE). Lanadelumab is a fully human monoclonal antibody (IgG1κ) targeting active plasma kallikrein. To support the efficacy and safety of lanadelumab for the proposed indication, the Applicant submitted the SPRING trial (Trial DX 2930-04-SHP643), a single-arm, pharmacokinetic (PK), pharmacodynamic (PD), and long-term safety clinical trial in 21 children 2 to < 12 years of age with type I or type II HAE. Completion of the SPRING trial also fulfills a Pediatric Written Request. The trial was divided in 2 periods (A and B) of 26 weeks each. During Period A, subjects 6 to <12 years of age received lanadelumab 150 mg subcutaneous (SC) every 2 weeks and subjects 2 to <6 years of age received lanadelumab 150 mg SC every 4weeks. During Period B, for subjects 6 to <12 years of age who were attack free during Period A, a reduction in dose frequency to 150 mg SC every 4 weeks was considered. Otherwise, subjects continued with the same dosing regimen during Period B.

Based on an overlap in the clinical presentation of both adult and pediatric HAE, consistency in the therapeutic approach, consistency of the lanadelumab mechanism of action, and relevance of the clinical endpoints, efficacy for children 2 to < 12 years of age is extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older. Extrapolation is supported by PK analyses demonstrating comparable systemic exposure for the proposed doses for children 2 to < 12 years of age (150 mg administered SC every 4 weeks for subjects 2 to <6 years and 150mg every 2 weeks for subjects 6 to <12 years with the option to increase to every 4 weeks for patients who are well-controlled on an every 2 week regimen) to the approved 300 mg dose (administered SC every 2 weeks or 4 weeks) in patients ≥12 year of age. The PD response was also comparable.

The safety profile of lanadelumab is well established since its approval in 2018 and includes a warning and precaution for hypersensitivity reactions and common adverse reactions of injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea. The safety profile in children 2 to < 12 years of age, as demonstrated in the submitted clinical trial, was similar to that observed in adults and adolescents 12 years of age and older. Except for danazol, an androgen with many adverse effects, lanadelumab proposes to be the first prophylactic HAE therapy for children less than 6 years of age. Of the injectable HAE prophylactic therapies, this supplement also introduces the first pre-filled syringe for use in children less than 12 years of age (current products are vials for SC or intravenous use). The overall risk-benefit is favorable for the approval of lanadelumab down to age 2 years for prophylaxis to prevent attacks of HAE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HAE is a rare, genetic condition caused by mutations in the SERPING1 gene, resulting in deficiency or dysfunction of C1-esterase inhibitor (C1-INH) protein. • Approximately 85% of patients have type I HAE, characterized by low production of normal C1-INH protein while the remaining 15% of patients have type II HAE, characterized by normal production and levels of dysfunctional C1-INH. • Absence of functional C1-INH leads to characteristic swelling of acute HAE attacks. • The exact prevalence is unknown, but HAE is estimated to affect 1 in 10,000 to 50,000 individuals worldwide (approximately 6,000 to 10,000 individuals in the U.S.). • Acute attacks of HAE are potentially life-threatening, particularly in cases of laryngeal edema resulting in airway compromise. Attacks at other anatomic sites (e.g., gastrointestinal tract, genitourinary tract, and skin) can cause disabling pain and significant morbidity. These attacks are unpredictable and highly variable in frequency and location among individuals and even within a given individual. • Although genetically present at birth, the disease may be clinically observable only many years later. In addition, variability of presentation and difficulty in diagnosis of the disease often lead to delayed recognition of the disorder. This, in turn, translates to difficulty in estimating the prevalence of symptomatic HAE, especially in the pediatric population, with any degree of certainty. • It has been estimated that 50-75% of patients have their first attack by the time they are 12 years of age. HAE attacks during infancy are	HAE is a rare, genetic, potentially life-threatening disease characterized by unpredictable, recurrent swelling attacks. Attacks are typically infrequent in pre-pubertal children. Early onset of symptoms and frequent attacks in childhood predict more severe disease in adulthood. Having a prophylactic agent for younger patients is critical given the impact on quality of life, productivity, anxiety, and absenteeism.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	considered rare. Furthermore, HAE attacks beginning at an early age may be associated with more severe phenotype of HAE.	
Current Treatment Options	• No cure exists; however, there are several approved therapies for prevention (i.e., prophylaxis) as well as treatment of acute attacks • Therapies for prophylaxis include plasma-derived C1-INH and oral attenuated androgens. C1-INH therapies have short half-lives and must be administered every 3-4 days intravenously or subcutaneously. Oral androgens are associated with numerous side effects that limit tolerability. • Prophylactic therapies do not eliminate all HAE attacks in all patients.	While there are approved prophylactic therapies for HAE patients, the availability of additional treatment options from a new pharmacologic class and with less frequent dosing is desirable for those unable to tolerate existing treatments or those with suboptimal response to available therapies, particularly to patients younger than 6 years who have limited prophylactic options available.
Benefit	• Based on an overlap in the clinical presentation of both adult and pediatric HAE, consistency in the therapeutic approach, consistency of the lanadelumab mechanism of action, and relevance of the clinical endpoints, efficacy for patients 2 to 11 years- of age is extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older with support from PK analyses showing similar drug exposure levels for 150 mg administered SC every 2-4 weeks and a similar PD response. The pediatric trial was not designed to assess efficacy given the small sample size, duration, and uncontrolled design. However, exploratory efficacy analyses were supportive. • Overall, the mean (SD) and median rate of investigator-confirmed HAE attacks decreased from 1.84 (1.525) and 1.44 attacks/month during the baseline observation period to 0.08 (0.170) and 0.00	Efficacy was extrapolated for patients 2-11 years of age from the adolescent and adult trials based on pharmacokinetic analyses showing similar drug exposure levels for 150 mg administered subcutaneously every 2 to 4 weeks, a similar pharmacodynamic response, and exploratory efficacy results from the pediatric trial. Lanadelumab would be the first biologic approved for prophylactic therapy for HAE patients between 2 to 6 years of age and would represent a clinically relevant, beneficial treatment for this difficult to treat patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	attacks/month at the end of the overall treatment period. Results were similar in both group of patients, independently of the dose frequency of administration.	
Risk and Risk Management	• The safety program for lanadelumab is well established since its approval in 2018 and includes a warning and precaution for hypersensitivity reactions and common adverse reactions of injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea. The safety profile in 2- to 11-year-olds was similar to that observed in adults and adolescents 12 years of age and older.	The risk analysis is similar to the approved indicated population.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO): Pediatric Quality of Life Inventory™ Generic Core Scale (PedsQL), Pediatric Quality of Life Inventory™ Family Impact Module (PedsQL-FIM), and EuroQoL 5-Dimension (EQ-5D-Y)	11.4.2: Health-related Quality of Life were considered exploratory endpoints 11.6.4 Health-related Quality of Life
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

HAE is a rare, autosomal dominant, inherited, potentially life-threatening disorder characterized by unpredictable attacks of angioedema.[1] HAE is caused by mutations in the SERPING1 gene, resulting in deficiency or dysfunction of C1-esterase inhibitor (C1-INH) protein, a serine protease inhibitor. Approximately 85% of patients have type I HAE, characterized by low production of normal C1-INH protein while the remaining 15% of patients have type II HAE, characterized by normal production and levels of dysfunctional C1-INH.[2] Absence of functional C1-INH leads to dysregulation of the contact system, a plasma protease cascade initiated by factor XII (FXII) that activates the proinflammatory kallikrein-kinin system and the procoagulant intrinsic coagulation pathway. Ordinarily, kallikrein activity is regulated by C1-INH, but in HAE patients kallikrein activity goes unchecked, leading to widespread release of bradykinin. In turn, bradykinin increases vascular permeability which leads to the characteristic swelling of acute HAE attacks.

It has been estimated that 50–75% of patients have their first attack by the time they are 12-years old.[3,4] Severe or life-threatening attacks do not occur as frequently in pediatric patients as they do in adults[4], however, between 3 and 6 years of age, and again around puberty, the frequency and severity of attacks may increase. Furthermore, HAE attacks beginning at an early age may be associated with a more severe phenotype of HAE.[6]

A significant unmet medical need for effective and safe treatment options exists among pediatric subjects with HAE. The unpredictable nature of HAE attacks in children results in significant decrements in vocational and school achievement, which poses a considerable burden on patients and their families.[7,8] Because of the impact that HAE has on quality of life, productivity, anxiety, and absenteeism, prophylactic agents are critical.

2.2. Analysis of Current Treatment Options

Medications used to treat HAE patients are typically categorized as treatments for acute attacks or prophylaxis. Although currently available treatments for routine prophylaxis of acute HAE attacks are effective in reducing the number and frequency of attacks, they do not eliminate all attacks in every individual. In addition to the FDA approved therapies shown in the **Table 1**, fresh frozen plasma (FFP) and antifibrinolytics (tranexamic acid, ε-aminocaproic acid) are available for HAE prophylaxis; however, with availability of more effective and targeted FDA approved therapies, their off-label use in HAE has declined and is no longer recommended.

Table 1: Summary of Treatment Armamentarium for HAE

Products	Pharmacologic Class	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Pediatric Indication
FDA Approved Treatments for Prophylaxis					
Danazol	Androgen	1980	200 mg PO BID-TID	Thromboembolism, hepatic dysfunction, hepatic adenoma, dyslipidemia, myopathy weight gain, acne, hirsutism, menstrual disturbance	No age limit
Cinryze	Plasma derived C1-INH	2008	1000 units IV every 3-4 days	Thromboembolism, hypersensitivity, transmissible infection	≥ 6 years
Haegarda	Plasma derived C1-INH	2017	60 IU/kg SC every 3-4 days	Same as Cinryze	≥ 6 years
Lanadelumab	Plasma kallikrein inhibitor	2018	300 mg SC every 2 weeks.	Hypersensitivity reactions, injection site reactions, transaminase elevations	>12 years
Orladeyo (Berotraslstat)	Plasma kallikrein inhibitor	2020	110-150 mg PO once daily	Abdominal pain, vomiting, diarrhea, back pain, gastroesophageal reflux disease	>12 years
FDA Approved Treatments for Acute Attacks					
Berinert	Plasma derived C1-INH	2009	20 IU/kg IV PRN	Same as Cinryze	No age limit
Kalbitor	Plasma kallikrein inhibitor	2009	30 mg SC PRN (Up to 60 mg/day)	Anaphylaxis	≥ 12 years
Firazyr	Bradykinin B2 Receptor antagonist	2011	30 mg SC PRN (Up to 90 mg/day)	Laryngeal attacks, injection site reactions, transaminase increase	≥ 18 years
Ruconest	Recombinant C1-INH	2014	50 units/kg IV (Max 4200units /dose	Thromboembolism, hypersensitivity	≥ 13 years

Source: Drugs@FDA.gov (https://www.accessdata.fda.gov/scripts/cder/daf/)
Abbreviations: BID: twice daily; C1-INH: C1 inhibitor; HAE: hereditary angioedema; IU: international units; IV: intravenous; Kg: kilogram; PO: oral; mg: milligram; PRN: as needed; SC: subcutaneously; TID: three times daily

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lanadelumab (marketed as TAKHZYRO®) was first approved for routine prophylaxis to prevent attacks of HAE in patients 12 years and older in the United States (US; August 23, 2018), Canada (September 19, 2018), and the European Union (EU; November 22,2018). 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; Trial 1 in the prescribing information]), and one phase 3 open label extension (OLE) study (Study DX-2930-04 [HELP Study Extension; Trial 2 in the prescribing information]).

3.2. Summary of Pre-submission/Submission Regulatory Activity

Lanadelumab (also referred to as DX-2930) was developed under IND 116647, which was opened on July 25, 2013. Lanadelumab was granted orphan drug designation on November 26, 2013, fast track designation on March 11, 2015, breakthrough therapy designation on July 2, 2015, and priority review designation on February 22, 2018. Lanadelumab was first approved on August 23, 2018, for patients with HAE aged 12 years or older. Orphan drug 7-year market exclusivity was granted for lanadelumab on September 24, 2018, for the treatment of HAE. A post marketing commitment (PMC 3466-1) was issued to submit the results of the ongoing open-label extension trial in adults and adolescents (SPRING Trial). The post marketing commitment fulfillment letter was issue on July 21, 2021.

Lanadelumab for treatment of HAE is exempt from Pediatric Research Equity Act (PREA) requirements due to the orphan drug designation. A Written Request (WR) was issued July 20, 2018 and amended on April 16, 2019. This sBLA presents data from a single, pivotal phase 3 pediatric study, SPRING Trial, that was conducted in accordance with the WR Amendment #1. With this sBLA, the Applicant also requested a Rare Pediatric Disease Priority Review Voucher.

A summary of topics related to the clinical development program that were discussed during key interactions between the Applicant and the FDA is provided below.

Table 2. Summary of Pre-Submission/Submission Regulatory Activity

Interaction	Date	Remarks
Proposed Pediatric Study Request	Mar 21, 2018	Written Request issued on July 20, 2018
Type C Meeting	November 8, 2018	FDA Suggested the following changes: Modified the pediatric dose regimen based on 2 cohort of patients: 6 to < 12 years and 2 to <6 years. Pediatric Written Request (PWR) needs to require a minimum number of patients to be studied in both age cohorts to obtain sufficient PK data for extrapolation of efficacy to the pediatric population.
Pediatric Revised Written Request	April 16, 2019	FDA suggested the following changes: Number of patients: A minimum of 5 patients in each cohort of 2 to 8 years of age and 9 to < 12 years of age. Delete injection site reactions as part of safety outcomes and adverse events of special interest. Dosage form and regimen according to age of the patient.
Communication with Applicant	June 12, 2019	FDA recommended to submit complete data to support extending the indication of lanadelumab to a new pediatric population for subsequent supplements to address the requirements of the PWR.

Abbreviations: PK: pharmacokinetics

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Office of Scientific Investigations (OSI) inspections were not deemed necessary for this supplement because the lanadelumab program was a multicenter trial with each site enrolling a small number of subjects.

4.2. Product Quality

Lanadelumab is a fully human IgG1/κ-light chain antibody that specifically binds and inhibits active plasma kallikrein proteolytic activity without binding pre-kallikrein, the circulating inactive precursor. Lanadelumab is produced in a recombinant Chinese Hamster Ovary (CHO) cell line and has an approximate molecular mass of 146 kD. The drug product, Takhzyro, is a sterile, preservative-free, colorless to slightly yellow solution supplied in 150 mg/1mL and 300 mg/2 mL single-dose vials. Each mL of ready-to-use Takhzyro solution contains lanadelumab (150 mg), citric acid monohydrate (4.1 mg), L-histidine (7.8 mg), polysorbate 80 (0.1 mg), sodium chloride (5.3 mg), sodium phosphate dibasic dihydrate (5.3 mg) and Water for Injection, USP. The solution has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg. The OBP review of this application recommends approval. Refer to the separate product quality reviews for additional details.

4.3. Devices and Companion Diagnostic Issues

The Applicant is proposing to add a new concentration of 150mg/mL provided as a 1 mL pre-filled syringe for a dosage strength of 150 mg for the younger pediatric population (2 to < 12 years of age). (b) (4) Doses for patients > 12 years of age (300 mg) come as single-dose 2 mL prefilled syringes (150mg/ml) and a 2 mL single-dose vial (150mg/ml). Device design verification and biocompatibility study results and assessments were reviewed by OBP and found to be acceptable. A CDRH review was not required for this simple pre-filled syringe.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

In Supplement #10, the Sponsor proposed to expand the use of TAKHZYRO in pediatric patients aged 2 to <12 years.

There is a complete nonclinical program for TAKHZYRO® that includes toxicology studies up to 39 weeks in monkeys and 4 weeks in rats. Studies in rats beyond 4 weeks were not feasible due to the formation of neutralizing ADA. No dose-limiting toxicity was identified in monkeys treated for up to 9 months. There were no DX-2930 related effects on male or female reproductive parameters in a 13-week repeat dose SC fertility study (once weekly dosing) conducted in sexually mature cynomolgus monkeys at doses of 10 or 50 mg/kg. In an enhanced pre- and post-natal development study, pregnant female cynomolgus monkeys were treated from GD 20 to delivery (approximately GD 163). There were no effects of DX-2930 treatment on maintenance of pregnancy or delivery. Furthermore, there were no effects of maternal DX-2930 treatment on behavioral, physical, or neurological measurements in F1 offspring that were followed for 3 months after delivery. It was judged that a juvenile monkey study to cover children from 2 to less than 12 years of age was not needed based upon inclusion of juvenile monkeys in the general toxicology studies as well as the results of ePPND study in monkeys that evaluated F1 offspring for up to 3 months after birth.

The intended commercial presentation for pediatric patients is a 1 mL pre-filled syringe (PFS) with a 150 mg dose. The components of the primary container closure system (CCS) are identical to the 2 mL PFS presentation. The extractables and leachables study for the 300 mg/2 mL PFS was reviewed previously under Supplement #3 (see Nonclinical Review submitted to DARRTS January 19, 2022).

Brief Discussion of Nonclinical Findings

The safety evaluation consisted of extractables study and leachables studies in support of the new 150 mg/1 mL PFS presentation.

The primary CCS consists of a glass syringe and a rubber stopper in contact with the drug product. The glass syringe barrel does not contribute organic leachables into the drug product; however, the rubber stopper has the potential to contribute organic leachables. The extractables and leachables studies were conducted with the primary CCS.

Extractables and leachables studies were conducted with the primary CCS. A leachables study was initiated to monitor potential leachables from the primary container closure into the aqueous drug product solution using long-term storage condition of 5±3°C throughout the intended shelf life, and at the accelerated storage condition of 25±2°C and 60±5% relative humidity (RH) over 6 months. For this study, both confirmed and identified extractables were

considered as potential leachables. Additionally, unidentified (b) (4) products detected in the extractables study are represented in the leachables study by (b) (4) and, in a separate study, (b) (4) were added as potential leachables because (b) (4) The leachables study is currently in progress. Testing results at T0/baseline, at 5±3°C after 12 months with an additional 2 weeks hold at 25±2°C, and at 25±2°C after 3 and 6 months of storage for three lots were provided in the submission.

The extractables and leachables from the 150 mg/1 mL PFS presentation did not appear to pose any safety concerns.

6. Clinical Pharmacology

6.1. Executive Summary

Lanadelumab is a fully human IgG1 monoclonal antibody that binds and inhibits plasma kallikrein. Kallikrein is an endogenous human serine protease responsible for generating cleaved high-molecular weight kininogen (cHMWK) and bradykinin, a potent vasodilator. Lanadelumab-flyo was approved in 2018 for prophylaxis to prevent attacks of HAE in patients 12 years and older. The current supplement intends to provide data supporting extension of the indication for patients aged 2 to < 12 years. The approved and proposed dosage regimens are summarized below:

Table 3. Dosage Regimens

Age Group	Approved Dosage Regimen
Adults and adolescents aged 12 and older	Administer 300 mg subcutaneously (SC) every 2 weeks (Q2W) Dosing every 4 weeks (Q4W) may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months Patients may self-administer
	Proposed Dosage Regimen
6 to < 12 years	Administer 150 mg SC Q2W Dosing Q4W may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months Healthcare provider or caregiver to administer
2 to < 6 years	Administer 150 mg SC Q4W Healthcare provider or caregiver to administer

Source: Approved and proposed labeling for TAKHZYRO [lanadelumab-flyo]

This supplement was supported by data from one 52-week, open-label phase 3 PK, PD, and safety trial in pediatric patients with type I or II HAE aged 2 to < 12 years (SPRING Trial). The study enrolled 17 subjects aged 6 to < 12 years and 4 subjects aged 2 to < 6 years. The Applicant also submitted a population PK and exposure-response report, and in-study bioanalytical reports for quantitation of PK, PD, and anti-drug antibodies (ADAs).

PK results from the SPRING trial indicate that lanadelumab exposures in the pediatric population 2 to < 12 years of age following administration of the proposed dosage regimens (150 mg Q2W for 6 to < 12 years; 150 mg Q4W for 6 to < 12 years who were well-controlled on a Q2W regimen; and 150 mg Q4W for 2 to < 6 years) are bracketed within the observed exposures in adults following administration of the two approved dosage regimens (i.e., 300 mg Q2W and 300 mg Q4W). PD results based on the percent change from baseline in cHMWK levels, a marker of plasma kallikrein enzymatic activity, suggest that changes in cHMWK levels following lanadelumab administration are similar between pediatric patients aged 2 to < 12 years, and adult/adolescent patients aged 12 years and older. The incidence of positive immunogenicity, based on observations of anti-lanadelumab antibodies, was 14.2% (3/21) in the SPRING Trial, including one patient positive for neutralizing antibodies (NAbs). Positive immunogenicity results appeared not to have impacts on efficacy, safety, PK, or PD.

An inspection request consult sent to the Office of Study Integrity and Surveillance (OSIS) was declined due to insufficient time for an inspection to be completed. The clinical pharmacology review team has determined that an OSIS inspection is not necessary for this BLA supplement for the following reasons:

- The bioanalytical method and site of analysis are the same as those used for analysis of PK data in the original BLA submission. At that time, the bioanalytical assay was found to be acceptable.
- Review of the SPRING trial in-study bioanalytical method and individual PK data did not raise specific concerns.
- PK data was analyzed using population PK incorporating data generated from the SPRING trial (submitted in the current BLA supplement), and from trials in adults and adolescents that were submitted to support approval in the original BLA submission.
- The SPRING trial was not a pivotal bioequivalence study.
- HAE is rare disease and this product haddresses an unmet medical need for prevention of HAE in patients aged 2 to < 6 years of age. In addition, the proposed product would be the only product approved for prevention of HAE available in an easier-to-use prefilled syringe presentation for patients 6 to < 12 years of age.

Recommendation: From a clinical pharmacology perspective, the data provided in this BLA supplement support approval of lanadelumab for prophylaxis to prevent attacks of HAE in pediatric patients aged 2 to < 12 years of age.

Post-marketing requirement/Post-marketing commitment: None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The following information is derived from the approved labeling for TAKHZYRO (lanadelumab-flyo):

The PK of lanadelumab was approximately dose-proportional in the therapeutic dose range in patients with HAE following SC administration. Peak plasma concentrations are reached within 5 days, and the terminal elimination half-life is approximately 2 weeks. The anticipated time to reach steady state was approximately 70 days. The mean accumulation ratio at steady state is approximately 1.44, 1.42, and 2.43 for dosing regimens of 150 mg Q4W, 300 mg Q4W, and 300 mg Q2W, respectively.

Table 4. Mean (SD) PK Parameters of Lanadelumab-Flyo Following SC Administration.

Pharmacokinetic Parameters	Lanadelumab-flyo		
	150 mg q4wks (N=28)	300 mg q4wks (N=29)	300 mg q2wks (N=27)
CL/F (L/day)	0.667 (0.162)	0.742 (0.239)	0.809 (0.370)
Vc/F (L)	14.1 (2.93)	14.9 (4.45)	16.6 (4.79)
$AUC_{tau,ss}$ (µg*day/mL)	233 (56.6)	441(137)	408 (138)
$C_{max,ss}$ (µg/mL)	12.0 (3.01)	23.3 (7.94)	34.4 (11.2)
$C_{min,ss}$ (µg/mL)	4.81 (1.40)	8.77 (2.80)	25.4 (9.18)
t_{max} (day)	5.17 (1.09)	5.17 (1.12)	4.11 (0.377)
$t_{1/2}$ (day)	14.9 (2.00)	14.2 (1.89)	15.0 (2.48)

Source: Approved labeling for TAKHZYRO [lanadelumab-flyo]
Abbreviations: $AUC_{tau,ss}$: area under the curve over the dosing interval at steady state; CL/F: apparent clearance; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; PK: pharmacokinetics; SC: subcutaneous; $t_{1/2}$: terminal elimination half-life; t_{max}: time to maximum concentration; Vc/F: apparent volume of distribution

No dosage adjustments were recommended for intrinsic or extrinsic factors. Body weight was identified as an important covariate to describe the variability in clearance and volume of distribution. Lighter-weight patients typically had higher lanadelumab exposure based on area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}). Pediatric patients aged 12 to <18 years administered a dosage regimen of 300 mg Q2W had a mean area under the curve at steady state (AUC_{ss}) that was approximately 37% higher than that determined in adults receiving the same regimen, likely due to the lower body weight in pediatric patients. Differences in lanadelumab exposure based on body weight were not considered to be clinically relevant and no dosage adjustments were recommended.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

As described in **Section 6.2.1**, patients with lower body weight tend to have greater lanadelumab exposures relative to patients with higher body weight. The doses evaluated in the SPRING Trial factored in the impacts of body weight and were selected to achieve lanadelumab exposures that would match exposures associated with the clinically efficacious approved dosage regimens in adults and adolescents. The doses evaluated in the SPRING Trial are the same doses proposed for marketing and include the following:

- 6 to < 12 years: 150 mg SC Q2W with the option to move to 150 mg Q4W if the patient is well-controlled
- 2 to < 6 years: 150 mg SC Q4W

The primary PK assessment was based on population PK modeling, which integrated all available data from adult and pediatric subjects, including data from the SPRING Trial, and from previously submitted trials DX-2930-01, DX-2930-02, DX-2930-03, and DX-2930-04. Adults were enrolled in all previously submitted studies, and adolescents were enrolled in trials DX-2930-03 and DX-2930-04. Results from population PK model simulations indicate that lanadelumab exposures in pediatric patients 2 to < 12 years at the proposed dosage regimens are bracketed within observed exposures in adults/adolescents following administration of the approved dosage regimens (i.e., 300 mg Q2W and 300 mg Q4W).

Therapeutic Individualization

As described above, the proposed dosage regimens in pediatric patients have factored in the effects of body weight known to impact lanadelumab exposure. Additional therapeutic individualization has not been proposed.

Outstanding Issues

From a clinical pharmacology perspective, there are no outstanding issues that would preclude approval of this BLA supplement.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant submitted data from one newly conducted clinical trial to support the use of lanadelumab in pediatric patients 2 to < 12 years of age. The SPRING Trial was a phase 3, open-label, multicenter, two-period, PK, PD, and safety study in pediatric patients with type I or type II HAE. The study enrolled 17 subjects aged 6 to < 12 years and 4 subjects aged 2 to < 6 years. Subjects entered a 52-week treatment period that was comprised of two 26-week treatment periods (A and B). The dosing regimen received was based on the subject's age at enrollment (i.e., 6 to < 12 years or 2 to < 6 years). All doses were administered SC in the abdomen, thigh, or upper arm.

- Treatment Period A: subjects aged 6 to < 12 years received 150 mg Q2W; subjects aged 2 to < 6 years received 150 mg Q4W
- Treatment Period B: subjects aged 6 to < 12 years could remain on the same regimen, or switch to a 150 mg Q4W regimen if well-controlled (i.e., attack free) for 26 weeks; subjects aged 2 to < 6 years continued to receive 150 mg Q4W.

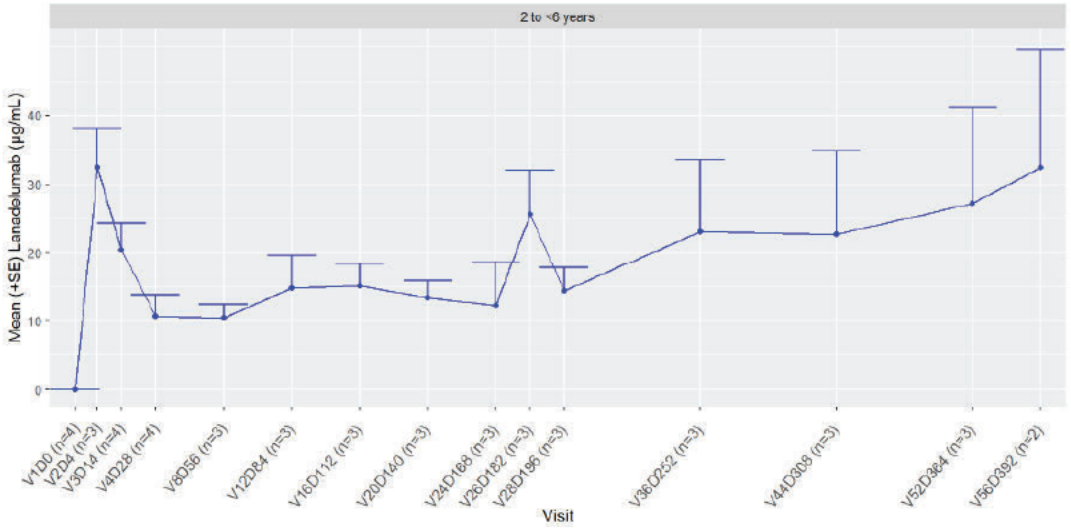
The primary objectives of the study were to evaluate the safety and PK of lanadelumab in children 2 to < 12 years of age with HAE. Secondary objectives included assessments of PD, based on plasma kallikrein activity, and immunogenicity. Evaluation of clinical outcomes was also a secondary objective based on the number of investigator-confirmed HAE attacks during the treatment period. For additional details on the design of the SPRING Trial, refer to Section 15.3.1.

The median [range] age of all enrolled subjects was 8.7 [3.5, 10.9] years. In the 2 to < 6 years and 6 to < 12 years age groups, the median [range] age was 4.5 [3.5, 5.3] years and 8.9 [6.0, 10.9] years, respectively. In the 2 to < 6 years age group, the median [range] body weight and median [range] body mass index (BMI) were 21.1 [15.8, 23.5] kg and 16.2 [15.3, 18.2] kg/m^2, respectively. In the 6 to < 12 years age group, the median [range] body weight and median [range] BMI were 31.1 [19.6, 63.3] kg and 17.8 [14.1, 30.5] kg/m^2, respectively.

Pharmacokinetics

In the SPRING Trial, PK was evaluated as a primary endpoint based on measurements of plasma trough concentrations over the treatment period. Plasma PK samples were collected at pre-dose on Days 0, 14 (Q2W dosing only), 28, 56, 84, 112, 140, 168, 182, 196, 252, 308, 364 (Week 52), and 392 (end of study). Additional samples were collected at any time of the day on Days 4, 14 (Q4W dosing only), and 182. The mean plasma lanadelumab concentration-time profiles is shown in Figure 1 and Figure 2, separated by age group and original treatment assignment. The figures summarize PK samples in all subjects, including for those with a change in dosing regimen after 26 weeks (i.e., in Treatment Period B). In the 6 to < 12 years age group, 7 out of 17 subjects (41.2%) switched from the 150 mg Q2W regimen to a 150 mg Q4W regimen in Treatment Period B. The protocol was not designed to permit subjects aged 2 to < 6 years to switch dosing regimens after 26 weeks. Nevertheless, 1 subject (25%) was switched from the 150 mg Q4W to the more frequent 150 mg Q2W regimen due to recurrent HAE attacks.

Figure 1. Mean ± SE Plasma Lanadelumab Concentrations Over Time in Patients 2 to < 6 Years of Age (N=4) Who Received 150 mg Q4W Lanadelumab.



D=day; n=number of subjects at each visit; q2wks=every 2 weeks; q4wks=every 4 weeks; SE=standard error; V=visit

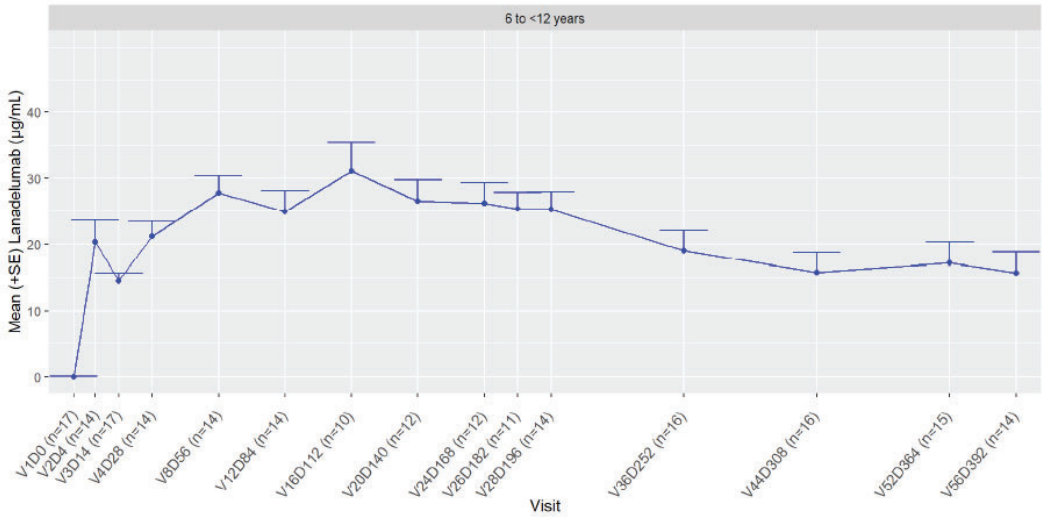
Notes: All concentrations were taken predose except for V2 (D4), V3 (D14), and V26 (D182).

Subject (b) (6) switched from 150 mg q2wks to 150 mg q2wks on V26 (D182) and is included in the above figure.

Source: SHIR-CSC-134-301, Figure 2 and SHP643-301 CSR, Figure 5.

Source: Figure 3, Summary of Clinical Pharmacology, BLA 761090 SDN 651

Figure 2. Mean ± SE Plasma Lanadelumab Concentrations Over Time in Patients 6 to < 12 Years of Age (N=17) Who Received 150 mg Q2W Lanadelumab.



D=day; n=number of subjects at each visit; q2wks=every 2 weeks; SE=standard error; V=visit

Notes: All concentrations were taken predose except V2 (D4), V3 (D14), and V26 (D182).

The concentration-time profile includes 7 subjects who originally received 150 mg q2wks and switched to 150 mg q4wks.

Source: SHIR-CSC-134-301, Figure 4 and SHP643-301 CSR, Figure 3.

Source: Figure 1, Summary of Clinical Pharmacology, BLA 761090 SDN 651

In subjects aged 2 to < 6 years of age, trough concentrations appear stabilized by Day 28, suggesting that steady state is reached at that time. The time profile also shows apparent increases in the mean lanadelumab trough concentration starting at Day 252 until the end of the study. Although there is variability in the measurements due to low sample size, the observed increase in trough concentration is likely driven by one subject ([redacted] (b) (6)) who was not well controlled on the originally assigned 150 mg Q4W regimen and was therefore switched to the more frequent 150 mg Q2W regimen on Day 182.

In subjects aged 6 to < 12 years of age, steady state is reached between Days 28 and 56. In contrast to the time profiles observed for subjects aged 2 to < 6 years, mean trough concentrations decrease starting at Day 252 through the end of the study. This is likely due to seven subjects who switched to the less frequent 150 mg Q4W regimen on Day 182 after remaining attack-free on the Q2W regimen during the initial treatment period.

Post-hoc PK parameter estimates for patients aged 2 to < 12 years of age were derived via population PK modeling. The Applicant's population PK model integrated all available data from adult and pediatric subjects, including data from the SPRING Trial, and from previously submitted trials supporting approval of the original BLA 761090, DX-2930-01, DX-2930-02, DX-2930-03, and DX-2930-04. Adults (n = 234) were enrolled in trials DX-2930-01, DX-2930-02, DX-2930-03, and DX-2930-04, while adolescents (n = 23) were enrolled in trials DX-2930-03 and DX-2930-04. Healthy subjects were enrolled in study DX-2930-01, while subjects with HAE were enrolled in trials DX-2930-02, DX-2930-03, and DX-2930-04. For additional details on the population PK methodology and analysis, refer to the Pharmacometrics Review in Section

15.3.3. Descriptive statistics of steady state lanadelumab exposure parameters separated by age group and derived from population PK analysis are shown in Table 5.

Table 5. Population PK-Derived Descriptive Statistics of Steady-State Lanadelumab Exposure Parameters in Pediatric Patients Age 2 to < 12 years, Separated by Age Group.

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

Source: SHIR-CSC-134-301, Table 7 and SHP643-301 CSR, Table 17

Source: Table 3, Summary of Clinical Pharmacology, BLA 761090 SDN 651

Table 6 shows a comparison of population PK-derived PK parameter estimates in pediatric patients 2 to < 12 years to reported PK parameters in adults and adolescents ≥ 12 years, as described in the current approved labeling of TAKHZYRO. Across populations and dosing regimens, time to maximum plasma concentration (T_{max}) and elimination half-life ($T_{1/2}$) are comparable. The steady state C_{min} and C_{ave} are also comparable across populations, with derived values in pediatric patients 2 to < 12 years falling approximately within those reported for adults and adolescents receiving approved dosage regimens of 300 mg Q4W or Q2W. Accounting for measures of variability, mean steady state C_{max} and AUC_{tau} also appear to be comparable between pediatric patients 2 to < 12 years of age and adults and adolescents ≥ 12 years of age, despite mean values being numerically greater for the youngest patients. When compared as steady state $AUC_{0\text{-}4wks}$, exposure in pediatric patients 2 to < 6 years of age

receiving 150 mg Q4W falls within exposures in adults and adolescents receiving dosage regimens of either 300 mg Q4W or Q2W. Steady state $AUC_{0\text{-}4wks}$ in pediatric patients 6 to < 12 years of age receiving 150 mg Q2W is approximately 1.2-fold greater relative to that in adults and adolescents on a regimen of 300 mg Q2W.

Table 6. Mean (SD) Steady State Lanadelumab PK Parameters in Pediatric Patients 2 to < 12 Years of Age, and Adults and Adolescents ≥ 12 Years of Age.

	Pediatric Patients 2 to < 12 Years		Adults and Adolescents ≥ 12 Years	
PK Parameter	**150 mg Q4W (N = 4)**	**150 mg Q2W (N = 17)**	**300 mg Q4W (N = 29)**	**300 mg Q2W (N = 27)**
$AUC_{tau,ss}$ µg*day/mL	719 (250)	492 165	441 (137)	408 (138)
$AUC_{0\text{-}4wks,ss}$* µg*day/mL	719 (250)	984 (330)	441 (137)	816 276
$C_{max,ss}$ µg/mL	39.0 (12.1)	41.6 14.6	23.3 (7.94)	34.4 (11.2)
$C_{ave,ss}$** µg/mL	25.7 (8.92)	35.2 (11.8)	15.8 (4.89)	29.1 9.86
$C_{min,ss}$ µg/mL	12.0 (5.34)	26.2 8.76	8.77 (2.80)	25.4 (9.18)
T_{max} (days)	5.08 (0.475)	3.77 (0.788)	5.17 (1.12)	4.11 (0.377)
$T_{1/2}$ (days)	11.9 (1.83)	13.5 (3.89)	14.2 (1.89)	15.0 (2.48)

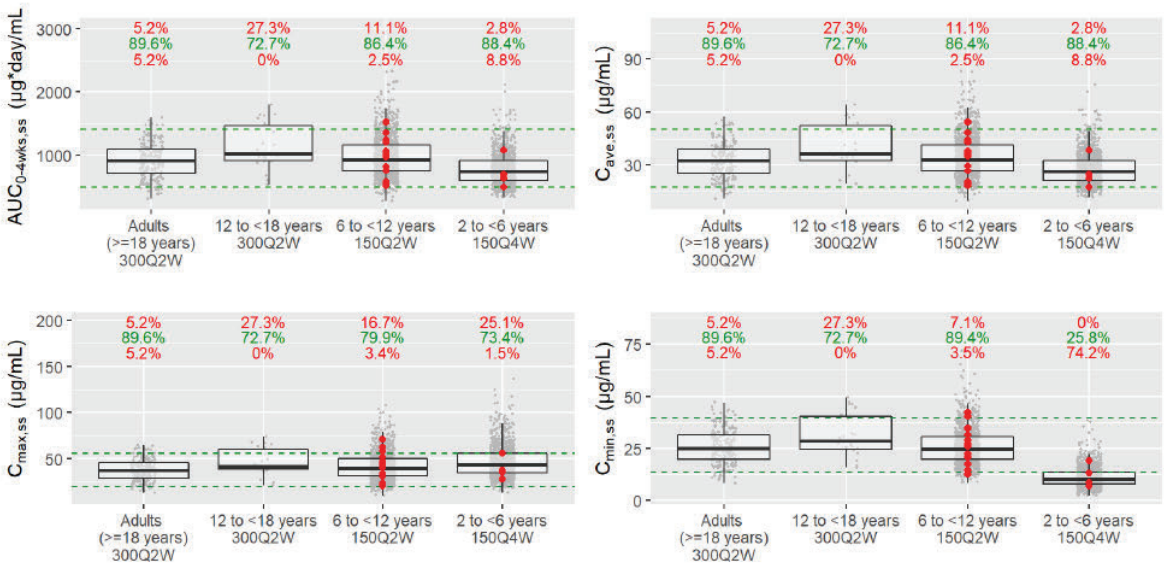
Source: Reviewer-generated table adapted from Table 3, Summary of Clinical Pharmacology, BLA 761090 SDN 651; and approved labeling for TAKHZYRO [lanadelumab-flyo]
*Values for $AUC_{0\text{-}4wks,ss}$ were determined as equal to $AUC_{tau,ss}$ for Q4W regimens, and as double $AUC_{tau,ss}$ for Q2W regimens.
**Values for $C_{ave,ss}$ for adults and adolescents ≥ 12 years were calculated as $AUC_{tau,ss}$ divided by the number of the days in the dosing interval (i.e., 28 days for Q4W regimens and 14 days for Q2W regimens).
Abbreviations: $AUC_{0\text{-}4wks,ss}$: area under the curve from 0 to 4 weeks at steady state; $AUC_{tau,ss}$: area under the curve over the dosing interval at steady state; $C_{ave,ss}$: average concentration at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; PK, pharmacokinetic; Q2W: every 2 weeks; Q4W: every 4 weeks; T_{max}: time to maximum concentration; $T_{1/2}$: terminal elimination half-life.

For subjects aged 6 to < 12 years who switched from the 150 mg Q2W regimen in Treatment Period A to the 150 mg Q4W regimen in Treatment Period B (n = 7) after Week 26, observed trough concentrations appear stabilized by Day 308 through the end of the study (Day 392), suggesting steady state is reached by Day 308 after the switch from Q2W to Q4W regimen. The observed mean (SD) lanadelumab trough concentrations measured at visits between Days 308 and 392 ranged from 6.81 (3.81) µg/mL to 7.96 (2.65) µg/mL. These observed concentrations are similar to slightly lower relative to the mean (SD) steady state $C_{min,ss}$ in adults and adolescents ≥ 12 years of age receiving lanadelumab 300 mg Q4W (Table 6). The data indicate that observed concentrations in pediatric subjects aged 6 to < 12 years that switch to a less frequent Q4W regimen still maintain lanadelumab concentrations comparable to those observed in adults and adolescents receiving the approved dosing regimen of 300 mg Q4W.

Due to the limited number of subjects enrolled in the SPRING Trial, the Applicant conducted model simulations to compare lanadelumab PK in pediatric populations relative to that in adults and adolescents. Simulations were conducted in a virtual pediatric population, including 1000 subjects each aged 2 to < 6 years and 6 to < 12 years. Post-hoc PK exposures and parameters

were derived from the virtual population and compared with those from adults and adolescents receiving 300 mg Q2W, as shown in Figure 3.

Figure 3. Boxplots of Lanadelumab Steady State Exposure Parameters Observed in Adults and Adolescents ≥ 12 Years Receiving 300 mg Q2W and Simulated in Virtual Pediatric Patients 2 to < 12 Years of Age Receiving 150 mg Q4W or 150 mg Q2W.

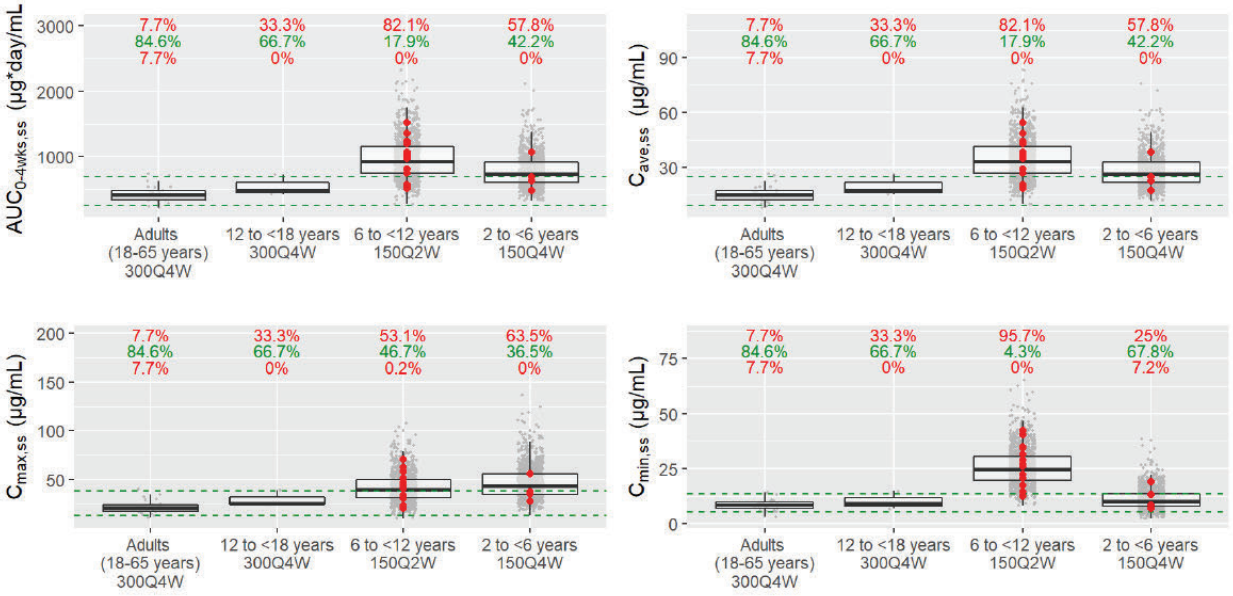


Source: Figure 10, Summary of Clinical Pharmacology, BLA 761090 SDN 651
Note that boxplots for adults and adolescents are based on data from the actual subjects enrolled in studies DX-2930-03 and DX-2930-04 who received 300 mg Q2W N 192 adults and N 22 adolescents). Boxplots for pediatric subjects 2 to < 12 years are based on data from simulated virtual subjects N 1000 each for 2 to < 6 years and 6 to < 12 years). Red circles laid over the boxplots of pediatric subjects 2 to < 12 years represent the parameters based on actual subjects enrolled in the SPRING Trial. Note that the lower and upper horizontal green dashed lines are the 5th and 95th percentiles of the reference data, 300 mg Q2W in adults. The red numbers represent the percentage above or below the reference range, while green numbers represent the percentage within the reference range.
Abbreviations: $AUC_{0\text{-}4wks,ss}$: area under the curve from 0 to 4 weeks at steady state; $C_{ave,ss}$: average concentration at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; Q2W: every 2 weeks; Q4W: every 4 weeks

Data in Figure 3 indicate that $AUC_{0\text{-}4wks}$, $C_{ave,ss}$, and $C_{max,ss}$ are comparable between adults and adolescents receiving 300 mg Q2W and pediatric patients 2 to < 12 years of age receiving either 150 mg Q4W or 150 mg Q2W. However, the data also indicate that the youngest patients aged 2 to < 6 years receiving 150 mg Q4W have lower $C_{min,ss}$, with approximately 74% of C_{trough} samples with a $C_{min,ss}$ falling below the 5th percentile of observed $C_{min,ss}$ in adults receiving 300 mg Q2W.

PK parameters from the virtual population were also compared with those from adults and adolescents receiving 300 mg Q4W, the other approved dosage regimen in adults and adolescents. This is shown in Figure 4.

Figure 4. Boxplots of Lanadelumab Steady State Exposure Parameters Observed in Adults and Adolescents ≥ 12 Years Receiving 300 mg Q4W and Simulated in Virtual Pediatric Patients 2 to < 12 Years of Age Receiving 150 mg Q4W or 150 mg Q2W.

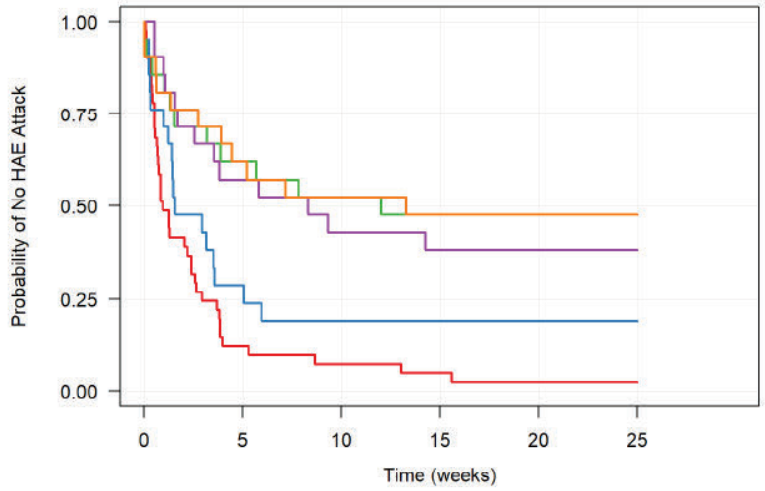


Source: Figure 3, Response to Clin Pharm IR, BLA 761090 SDN 665
Note that boxplots for adults and adolescents are based on data from the actual subjects enrolled in studies DX-2930-03 who received 300 mg Q4W N 26 adults and N 3 adolescents). Boxplots for pediatric subjects 2 to < 12 years are based on data from simulated virtual subjects N 1000 each for 2 to < 6 years and 6 to < 12 years). Red circles laid over the boxplots of pediatric subjects 2 to < 12 years represent the parameters based on actual subjects enrolled in the SPRING Trial.
Note that the lower and upper horizontal green dashed lines are the 5th and 95th percentiles of the reference data, 300 mg Q4W in adults. The red numbers represent the percentage above or below the reference range, while green numbers represent the percentage within the reference range.
Abbreviations: $AUC_{0\text{-}4wks,ss}$: area under the curve from 0 to 4 weeks at steady state; $C_{ave,ss}$: average concentration at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration at steady state; Q2W: every 2 weeks; Q4W: every 4 weeks

Data in Figure 4 indicate that the majority of pediatric patients aged 2 to < 12 years receiving 150 mg Q4W or 150 mg Q2W have higher $AUC_{0\text{-}4wks}$, $C_{ave,ss}$, and $C_{max,ss}$ relative to those from adults and adolescents receiving 300 mg Q4W. This is expected given that these parameters were comparable when compared to adults and adolescents on the 300 mg Q2W regimen. $C_{min,ss}$ was also greater for patients 6 to < 12 years receiving 150 mg Q2W when compared to adults and adolescents receiving 300 mg Q4W. For patients aged 2 to < 6 years receiving 150 mg Q4W, $C_{min,ss}$ is comparable to those observed in adults and adolescents, with approximately 68% of C_{trough} samples having a $C_{min,ss}$ falling within the 5th and 95th percentiles of observed $C_{min,ss}$ in adults receiving 300 mg Q4W.

The Applicant conducted exposure-response analyses in adults and adolescents evaluating the time to first HAE attack as a function of lanadelumab exposure parameter quartiles. Results of the analyses indicated a relationship between C_{ave} quartile and time to first HAE attack (Figure 6). However, the relationship was less clearly demonstrated with C_{min} (Figure 5). Exposure-response analyses in adults and adolescents based on $C_{min,ss}$ quartiles and $C_{ave,ss}$ quartiles are shown in Figure 5 and Figure 6, respectively.

Figure 5. Time to First HAE Attack as a Function of Lanadelumab $C_{min,ss}$ Quartiles in Adults and Adolescents in Study DX-2930-03.

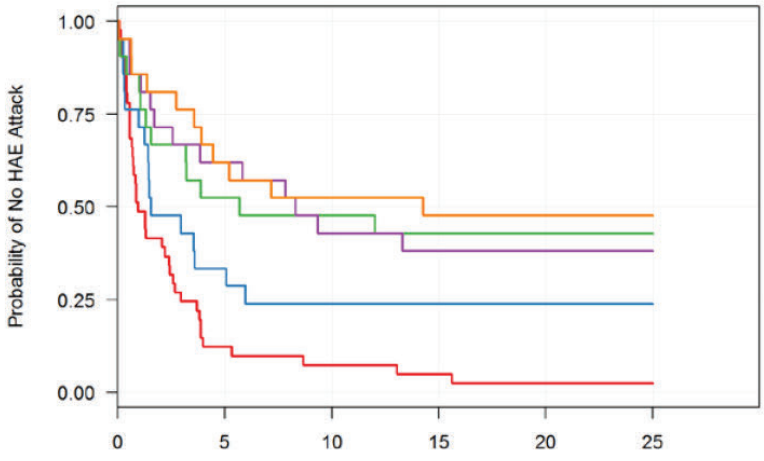


							Median Time to First HAE Attack (95% CI)
Placebo	41	5	3	2	1	1	0.950 (0.712, 2.41)
1st quartile of Cmin [2.47, 5.01)	21	6	4	4	4	4	1.56 (1.23, 5.97)
2nd quartile of Cmin [5.01, 8.02)	21	13	11	10	10	10	12.0 (3.20, NA)
3rd quartile of Cmin [8.02, 17.6)	21	12	9	8	8	8	8.30 (2.56, NA)
4th quartile of Cmin [17.6, 41.2]	21	13	11	10	10	10	13.3 (3.90, NA)

Source: Figure 1, Response to Clin Pharm IR, BLA 761090 SDN 665
Abbreviations: $C_{min,ss}$: minimum plasma concentration at steady state; HAE: hereditary angioedema

When evaluated as a function of $C_{min,ss}$ quartiles, worse efficacy was observed for subjects that fell into the lowest $C_{min,ss}$ quartile (range of 2.48 to < 5.01 µg/mL). Meanwhile, no apparent relationship in the median time to first HAE attack was observed among the remaining quartiles (i.e., 2nd to 4th quartiles), suggesting no meaningful difference in efficacy observed among subjects in higher $C_{min,ss}$ quartiles. Notably, the estimated $C_{min,ss}$ in pediatric patients aged 2 to < 12 years ranged from 6.98 to 42.2 µg/mL. Thus, all pediatric subjects would fall above the lowest $C_{min,ss}$ quartile. The results suggest that there is not likely to be an impact on efficacy due to reduced Cmin,ss in pediatric patients 2 to < 6 years receiving 150 mg Q4W relative to adults and adolescents receiving 300 mg Q2W.

Figure 6. Time to First HAE Attack as a Function of Lanadelumab $C_{ave,ss}$ Quartiles in Adults and Adolescents in Study DX-2930-03.



							Median Time to First HAE Attack (95% CI)
Placebo	41	5	3	2	1	1	0.950 (0.712, 2.41)
1st quartile of Cave [5.24, 9.00)	21	7	5	5	5	5	1.56 (1.23, NA)
2nd quartile of Cave [9.00, 14.2)	21	11	10	9	9	9	5.69 (1.55, NA)
3rd quartile of Cave [14.2, 22.4)	21	13	9	8	8	8	8.30 (2.56, NA)
4th quartile of Cave [22.4, 47.6]	21	13	11	10	10	10	14.3 (3.90, NA)

Source: Figure 19, Population PK Report, BLA 761090 SDN 651
Abbreviations: $C_{ave,ss}$: average plasma concentration at steady state; HAE: hereditary angioedema; NA: not applicable

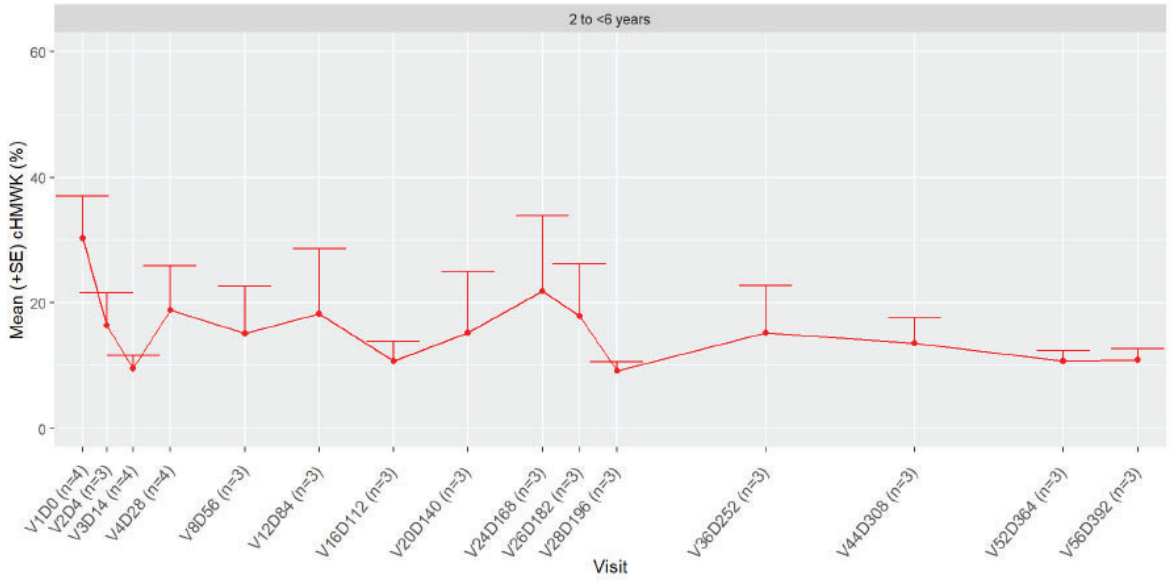
In contrast to observations using $C_{min,ss}$ quartile, a clearer relationship was demonstrated between $C_{ave,ss}$ quartiles and median time to first HAE attack, with the median time to first HAE attack increasing with increasing $C_{ave,ss}$ quartile. The estimated $C_{ave,ss}$ in pediatric patients 2 to < 12 years of age ranged from 17.3 to 54.5 µg/mL. Thus, all pediatric subjects would fall within and beyond the 3rd and 4th $C_{ave,ss}$ quartiles.

Overall, results indicate that exposures in the pediatric population 2 to < 12 years of age after receiving the proposed lanadelumab dosage regimens of 150 mg Q4W or 150 mg Q2W are bracketed within the exposures observed following administration of the two approved dosage regimens in adults and adolescents. The exposure-response analyses established in adults and adolescents using the median time to first HAE attack against $C_{min,ss}/C_{ave,ss}$ quartiles also support the proposed pediatric dosing regimens.

Pharmacodynamics

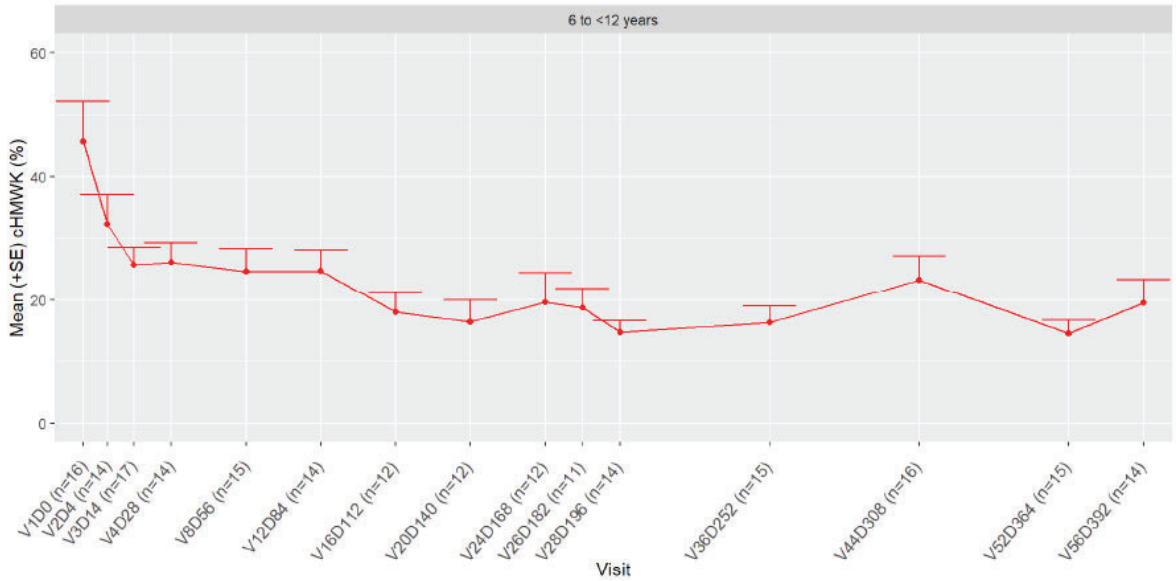
In the SPRING Trial, PD was assessed as a secondary objective, based on measurements of plasma cHMWK as a measure of plasma kallikrein enzymatic activity. Plasma PD samples for measurement of cHMWK (secondary objectives) were collected pre-dose on Days 0, 28, 56, 84, 112, 140, 168, 196, 252, 308, 364, and 392. Additional samples were collected at any time of the day on Days 4, 14, and 182. The mean time profiles for percent cHMWK is shown in Figure 7 and Figure 8, separated by age group and original treatment assignment. The figures summarize PD in all subjects, including for those with a change in dosing regimen after 26 weeks (i.e., in Treatment Period B).

Figure 7. Mean ± SE Time Profile for Percent cHMWK in Patients 2 to < 6 Years of Age Who Received 150 mg Q4W Lanadelumab.



Source: Figure 7, Summary of Clinical Pharmacology, BLA 761090 SDN 651
Abbreviations: cHMWK: cleaved high molecular weight kininogen; D: day; Q4W: every 4 weeks; SE: standard error; V: visit

Figure 8. Mean ± SE Time Profile for Percent cHMWK in Patients 6 to < 12 Years of Age Who Received 150 mg Q2W Lanadelumab.



Source: Figure 5, Summary of Clinical Pharmacology, BLA 761090 SDN 651
Abbreviations: cHMWK: cleaved high molecular weight kininogen; D: day; Q2W: every 2 weeks; SE: standard error; V: visit

In subjects aged 2 to < 6 years, the mean percent cHMWK decreased from the baseline after the first dose and the suppression appeared stabilized around Day 14 and maintained throughout the study. By the end of the study (Day 392), the mean (standard error [SE]) and median percent change from baseline in cHMWK was -64.7 (5.9)% and -70.0%, respectively. The time profile for subjects aged 2 to < 6 years shows variability through Day 182, then appears to level off until the end of the study. The variability may be partly due to low sample size (n = 3 to

4) at each time point. However, the variability also appears to be driven by one subject ((b) (6) who was not well controlled on the originally assigned 150 mg Q4W regimen. This subject was switched to the more frequent 150 mg Q2W regimen on Day 182, after which markedly less variability is observed.

In subjects aged 6 to < 12 years, the mean percent cHMWK decreased from the baseline after the first dose and the suppression appeared stabilized around Day 14 and maintained throughout the study. There is no marked change in the profile even after some subjects in this age group switched to the less frequent 150 mg Q4W regimen. By the end of the study (Day 392), the mean (SE) and median percent change from baseline in cHMWK was -50.4 (13.0)% and -65.1%, respectively.

Data in adults and adolescents is derived from pivotal study DX-2930-03, which was previously submitted to support original approval of BLA 761090 (*Data derived from PK and PD Data Summarization for Trial DX-2930-03, BLA 761090 SDN 5*). By the end of the trial (Day 182), the mean (SE) and median percent change from baseline in cHMWK in adults and adolescents receiving a dosage regimen of 300 mg Q2W was -46.4 (8.0)% and -63.5%, respectively. The mean (SE) and median percent change from baseline in cHMWK in adults and adolescents receiving 300 mg Q4W was -48.2 (3.7)% and -52.7%, respectively.

The percent change from baseline in cHMWK by population is summarized in Table 7. Data indicate that the percent change from baseline in cHMWK in patients aged 2 to < 12 years receiving their respective proposed lanadelumab dosage regimens is comparable to that observed in adults and adolescents receiving the approved lanadelumab dosage regimens of 300 mg Q2W or Q4W.

Table 7. Mean (SE) and Median Percent Change From Baseline in cHMWK by Age Group at the End of the SPRING Trial and Trial DX-2930-03.

Age Group	N	Dosage Regimen	Mean (SE) (%)*	Median (%)*
2 to < 6 years	3	150 mg Q4W	-64.7 5.9	-70.0
6 to < 12 years	13	150 mg Q2W	-50.4 (13.0)	-65.1
Adults and adolescents ≥ 12 years	26	300 mg Q4W	-48.2 (3.7)	-52.7
Adults and adolescents ≥ 12 years	28	300 mg Q2W	-46.4 8.0	-63.5

Source: Reviewer-generated table adapted from Section 12.3 and 12.4, Population PK Report for SPRING Trial, BLA 761090 SDN 651; and Tables 14.9 and 14.10, PK and PD Data Summarization for Study DX-2930-03, BLA 761090 SDN 5
Note that the number of subjects represented from the 2 to < 12 years age group in SPRING Trial only included those for which data was available at the end of the study (Day 392).
*Mean (SE) and median values for pediatric patients aged 2 to < 6 years and 6 to < 12 years were derived from data collected on Day 392 (end of SPRING Trial). Mean (SE) and median values for adults and adolescents aged 12 years and older were derived from data collected on Day 182 (end of trial DX-2930-03).
Abbreviations: cHMWK: cleaved high molecular weight kininogen; Q2W: every 2 weeks; Q4W: every 4 weeks; SE: standard error

C1 esterase inhibitor (C1-INH) and complement 4 (C4) plasma concentrations were also measured in the SPRING Trial as exploratory PD biomarkers. In subjects aged 2 to < 6 years assigned to receive 150 mg Q4W, C1-INH decreased from a mean (standard deviation [SD]) of 153.6 (134.2) mU/mL at baseline to 91.1 (58.7) mU/mL at the end of the study (Day 392). C1-INH reductions were more modest for subjects aged 6 to < 12 years assigned to receive 150 mg Q2W. C1-INH decreased from a mean (SD) of 116.9 (30.5) mU/mL at baseline to 91.9 (32.5)

mU/mL at the end of the study (Day 392). The clinical meaning of reduction of plasma C1-INH from baseline is unclear.

Little changes in C4 concentrations were observed during the SPRING Trial. In subjects aged 2 to < 6 years (150 mg Q4W), C4 decreased from a mean (SD) of 73.4 (22.8) µg/mL at baseline to 59.4 (1.1) µg/mL at the end of the study (Day 392). In subjects aged 6 to < 12 years (150 mg Q2W), C4 did not appear to decrease during the SPRING Trial. The mean (SD) was 78.9 (24.1) µg/mL at baseline and 73.6 (15.6) µg/mL at the end of the study (Day 392).

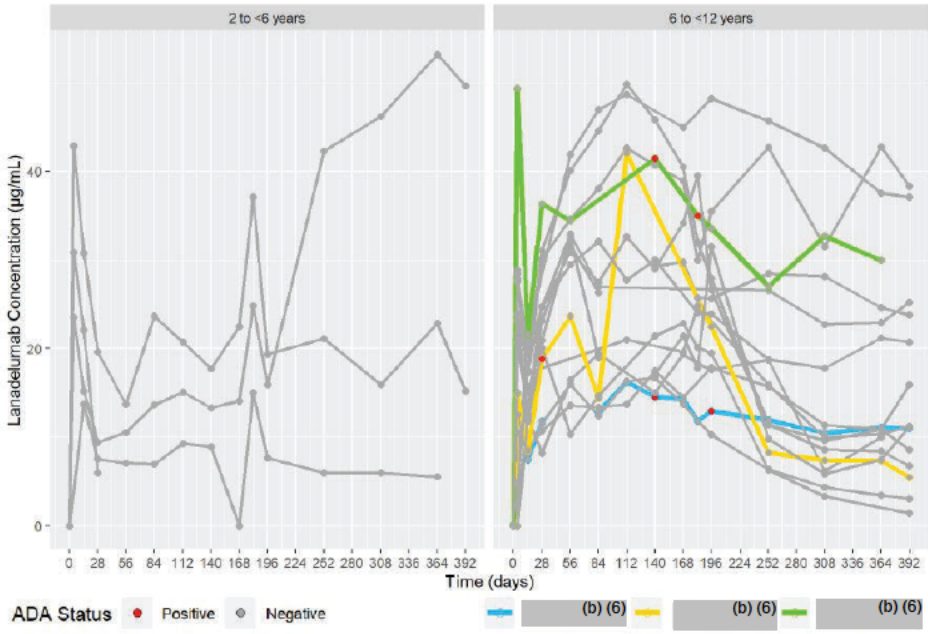
Immunogenicity

Immunogenicity was assessed in the SPRING Trial. Plasma samples for assessment of anti-drug antibodies (ADAs) were collected pre-dose on Days 0, 28, 84, 140, 182, 196, 252, 308, 364, and 392.

Out of 21 subjects, 3 (14.2%) developed ADAs to lanadelumab, based on 5 out of 182 (2.7%) confirmed-positive immunogenicity samples. All 3 subjects were in the 6 to < 12 years age group receiving a dosage regimen of 150 mg Q2W. One subject also presented with neutralizing antibodies. Subjects confirmed anti-drug antibody (ADA)-positive did not remain ADA-positive for the duration of the study. All individual ADA profiles were transient and were not present for more than two consecutive time points.

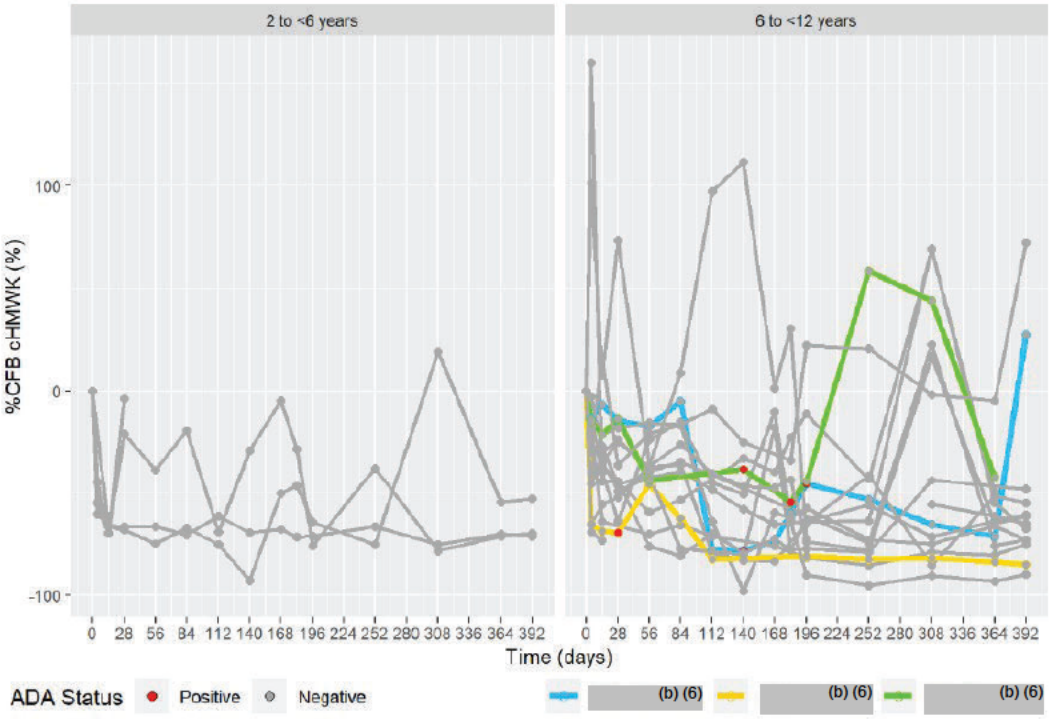
Immunogenicity status appeared not to have impacts on PK or PD, as shown in Figure 9 and Figure 10. Data indicate that lanadelumab concentrations in confirmed ADA-positive subjects were within the range of those observed in ADA-negative subjects. PD data, based on the percent change from baseline in cHMWK also appeared similar among ADA-positive vs. ADA-negative subjects.

Figure 9. Observed Individual Lanadelumab Concentrations Over Time by ADA Status.



Source: Figure 15, Summary of Clinical Pharmacology, BLA 761090 SDN 651
Note: Lines in color represent subjects that were confirmed ADA-positive over the course of the study. Red dots indicate the time point at which the presence of ADAs was confirmed.
Abbreviations: ADA: anti-drug ant body

Figure 10. Observed Individual Percent Change From Baseline in cHMWK Over Time by ADA Status.



Source: Figure 16, Summary of Clinical Pharmacology, BLA 761090 SDN 651
Note: Lines in color represent subjects that were confirmed ADA-positive over the course of the study. Red dots indicate the time point at which the presence of ADAs was confirmed.
Abbreviations: ADA: anti-drug ant body; CFB: change from baseline; cHMWK: cleaved high molecular weight kininogen

Based on the limited available data, immunogenicity status appeared not to have any apparent impacts to efficacy. None of the ADA-positive subjects experienced an HAE attack over the course of study (both Period A and B), and 1 subject switched to a less frequent Q4W regimen in Treatment Period B (i.e., after remaining stably attack-free for 26 weeks of treatment on the 150 mg Q2W regimen).

Immunogenicity status also did not have any apparent impacts on safety and was not associated with an increased rate of hypersensitivity events. One out of 3 (33%) ADA-positive subjects experienced one hypersensitivity event of mild severity compared to 3 out of 14 (21.4%) ADA-negative subjects aged 6 to < 12 years of age who experienced six hypersensitivity events. Of note 2 out of 4 (50%) subjects in the 2 to < 6 years age group, none of whom were confirmed ADA-positive, experienced three hypersensitivity events.

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

This submission includes data from one clinical trial, SPRING Trial, to support the use of lanadelumab in pediatric patients 2 to < 12 years of age. The SPRING Trial was conducted in an open-label manner. As a result, the primary objectives of the study were to evaluate the safety and PK, while evaluation of clinical outcomes was a secondary objective based on the number of investigator-confirmed HAE attacks during the treatment period. Refer to Section 8 for assessment of efficacy in the SPRING Trial.

Exposure-response analyses in adults and adolescents indicated that the median time to first HAE attack increases with increasing $C_{ave,ss}$ quartile. A less clear relationship was observed with $C_{min,ss}$ in which subjects falling into the lowest quartile had worse efficacy, while there was no apparent relationship in the median time to first HAE attack among the 2nd to 4th quartiles. Refer to Figure 5 and Figure 6 in Section 6.3.1 for additional details.

The estimated $C_{min,ss}$ values in pediatric patients 2 to < 12 years of age (6.98 to 18.9 µg/mL) are within the 2nd to 4th $C_{min,ss}$ quartiles determined in adults and adolescents. The estimated $C_{ave,ss}$ values (17.3 to 54.5 µg/mL) are within and beyond the 3rd and 4th $C_{ave,ss}$ quartiles determined in adults and adolescents. The exposure-response analyses established in adults and adolescents using the median time to first HAE attack against $C_{min,ss}/C_{ave,ss}$ quartiles also support the proposed pediatric dosing regimens.

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Results from population PK model simulations indicate that lanadelumab exposures at the proposed dosage regimens (150 mg Q4W in pediatric patients aged 2 to < 6 years and 150 mg Q2W in pediatric patients aged 6 to < 12 years) are bracketed within observed exposures in adults following administration of the approved dosage regimens (i.e., 300 mg Q2W and 300 mg Q4W). Therefore, the proposed dosage regimens are appropriate for pediatric patients aged 2 to < 12 years.

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

No alternative dosing regimen or management strategy is proposed for subpopulations based on intrinsic patient factors.

Per the currently approved labeling for lanadelumab, body weight was identified as an important covariate to describe the variability in clearance and volume of distribution. At the same dose, lighter weight patients typically have higher lanadelumab exposure (C_{max} and AUC) relative to heavier weight patients. Pediatric patients aged 12 to < 18 years administered a dosage regimen of 300 mg Q2W had a mean AUC_{ss} that was approximately 37% higher than that determined in adults receiving the same regimen. Despite this, there was no observed difference in the relationship between lanadelumab concentrations and cHMWK levels in adults and adolescents. The difference in exposure was not considered clinically relevant and no dosage adjustments were recommended. Per the original BLA review for lanadelumab (BLA 761090), no other demographic characteristics, including age, race, or sex, have a relevant effect on the PK of lanadelumab after correcting for body weight.

In the SPRING Trial, the doses evaluated factored in the impacts of body weight and were selected to achieve lanadelumab exposures that would match exposures associated with the clinically efficacious approved dosage regimens in adults and adolescents (300 mg Q2W). These include a dosage regimen of 150 mg Q2W for pediatric patients aged 6 to < 12 years, and 150 mg Q4W for pediatric patients aged 2 to < 6 years. These dosage regimens evaluated in the SPRING Trial are the same as those proposed for marketing.

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Lanadelumab is administered via SC injection. Therefore, there are no clinically relevant food-drug interactions. The current approved labeling for lanadelumab indicates that no dedicated drug interaction studies have been conducted. In addition, the labeling describes that the use of analgesic, antibacterial, antihistamine, anti-inflammatory, and anti-rheumatic medications had no effect on the clearance and volume of distribution of lanadelumab. No new data was submitted in this sBLA regarding drug-drug interactions.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The sources of clinical data used in this review are summarized in the table below.

Table 8. Clinical Trial Relevant to this sBLA

Trial Identity	Trial Design	Regimen (mg)*	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled phase 3 studies to support efficacy and safety							
SPRING Trial DX 2930-04-SHP643 08/19/2019-10/30/2021	Open label, single arm	Period A: • 150 mg Q4W (2yo to <6yo) • 150 mg Q2W 6 yo to < 12 yo Period B: • 150 mg Q4W (2yo to <6 yo) • 150 mg Q2W 6 yo to < 12 yo **	Safety, PK, PD Immunogenicity, # HAE attacks Efficacy (descriptive)	52 weeks/ 2-4 weeks	24 screened 21 treated 20 completed	2 to < 12 years of age	17 sites U.S., Canada, Spain, Hungary, Germany

Source:
*All doses administered subcutaneously
**Subjects 6 to <12 years of age were to receive lanadelumab 150 mg q2wks in Treatment Period A and could have remained on the same dose regimen in Treatment B or, if the subjects had been well controlled (e.g., attack-free) for 26 weeks, the subjects could switch to a dose of 150 mg q4wks
Abbreviations: DB: double-blind, HAE: hereditary angioedema, MAD: multiple ascending doses, OLE: open label extension, PC: placebo-controlled, PG: parallel group, PD: pharmacodynamics, PK: pharmacokinetic, Q2W: every 2 weeks, Q4W: every 4 weeks, R: randomized, yo: years old

7.2. Review Strategy

This supplement review contains one trial (SPRING) evaluating PK, PD, and safety endpoints in subjects 2 to <12 years of age. The clinical review was conducted by one primary clinical reviewer and one statistical reviewer. Efficacy was evaluated under the original BLA (approved August 2018) for ages 12 years and older. SPRING Trial was not designed or powered to detect significant changes in the clinical assessments, but the trial had secondary efficacy endpoints and exploratory patient reported outcome endpoints which are briefly discussed in Section 8.2.6. For the evaluation of safety, FDA medical officer Dr. Diana Nichols-Vinueza analyzed data from Trial DX-2930-04 using JMP, JMP Clinical, and Analysis Studio. The safety results presented in Section 8.2 represent the medical office reviewer's own analyses.

Additionally, Internal FDA Subject Matter Expert (SME) Team assisted in the independent production of tables through commonly used clinical data review tools, including production of specialized tables. This service included review of tables provided by the Applicant with an in-depth assessment of the clinical data.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. SPRING Trial

8.1.1.1. Administrative Information

- **Study 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
- **Study Dates:** Initiation date, August 19, 2019; study completion date, October 30, 2021
- **Study Sites:** Canada, Germany, Hungary, Spain, United States.
- **Study Report Date:** June 29, 2022

8.1.1.2. Objectives

Primary Objective

To evaluate the safety and PK of lanadelumab in pediatric subjects (2 to <12 years of age) with HAE.

Secondary Objectives

- To evaluate the clinical activity/outcomes (hereafter referred to as clinical outcomes) of lanadelumab in preventing HAE attacks in pediatric subjects (2 to <12 years of age) with HAE.
- To characterize the PD of lanadelumab in pediatric subjects (2 to <12 years of age) with HAE.
- To assess the immunogenicity of chronically administered lanadelumab and its effect on PK, PD, clinical outcomes, and safety in pediatric subjects (2 to <12 years of age) with HAE.

Exploratory Endpoints

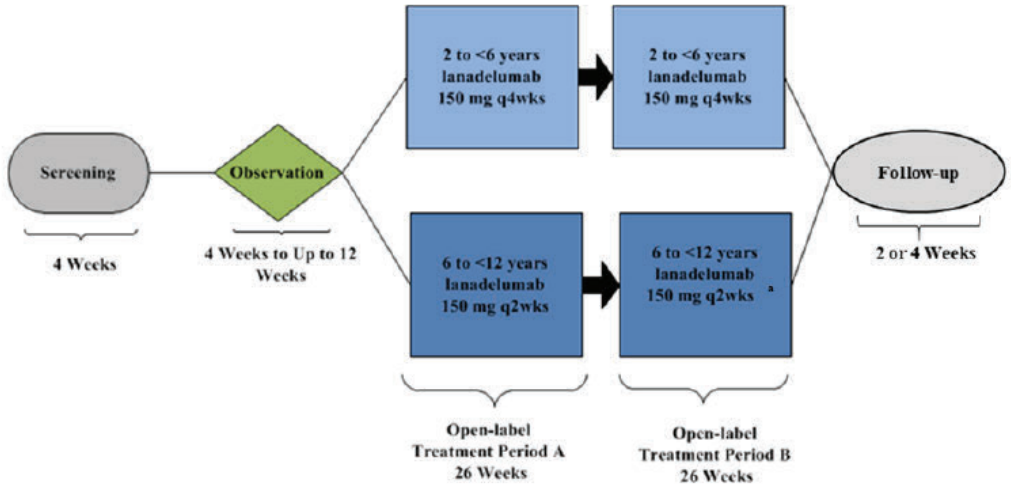
- To evaluate the effect of lanadelumab on health-related quality of life (HRQoL)
- To evaluate the effect of lanadelumab on C1-INH, complement 4 (C4), and exploratory biomarker(s) of angioedema disease-state bioactivity.

8.1.1.3. Study Design

8.1.1.3.1. Trial Design

This was an open-label, uncontrolled, multicenter study designed to evaluate the safety, PK, PD, and the clinical outcomes of lanadelumab in preventing acute attacks of type I and type II HAE in pediatric subjects. Following inform consent, subjects aged 2 to <12 years of age underwent a 2-week washout period of long-term prophylactic therapies (e.g., C1-INH replacements, attenuated androgens) to ensure that their disease could be adequately treated with on-demand therapy before entering this period. Subjects not currently taking long term prophylaxis did not require the 2-week washout period. Following screening, subjects entered an observation period of 4 weeks (up to 12 weeks) to ensure a robust evaluation of baseline attack rate. Subjects meeting a minimum baseline rate of at least one investigator-confirmed HAE attack (per 4 weeks) during the observation period were eligible for enrollment. Subjects not meeting the minimum attack rate during the first 4 weeks were allowed to extend the observation period for another 8 weeks (12 weeks total). Subjects experiencing two or more attacks during the observation period were allowed to exit this period early. Eligible subjects receive lanadelumab treatment for 26 weeks (Treatment Period A). This trial was extended for another 26 weeks of treatment (Treatment Period B) with the goal of collecting long-term safety data in this pediatric population; study visits occurred every 2 weeks. Following treatment, subjects entered a 2- or 4-weeks follow-up period. A schematic of the trial design and table of the trial assessments are shown below in Figure 11, Figure 12 (Period A) and Figure 13 (Period B).

Figure 11: Study Design Schematic: SPRING Trial



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.

Source: SPRING Trial protocol, Figure 1, p37

Figure 12: Schedule of Activities- Treatment Period A (Week1 To Week 26)

	Treatment Period Shaded columns: scheduled onsite visits Nonshaded columns: potential subject-elected offsite activity																									
Study Week	1-2		3-4		5-8				9-12				13-16				17-20				21-24				25-26	
Study Visit (± 4 days)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Study Day	0	4	14	28	35	42	49	56	63	70	77	84	91	98	105	112	119	126	133	140	147	154	161	168	175	182
Confirmation of eligibility	X																									
Prior/current medications, therapies, and procedures	X																									
Vital signs[a]	X		X	X				X				X				X				X				X		
Physical examination[b]	X		X	X				X				X				X				X				X		
Hematology, serum chemistry, and coagulation tests	X			X				X				X				X				X				X		
Pregnancy testing[c]	X							X								X								X		
Plasma PK sample[d]	X	X	X	X				X				X				X				X				X		X
Plasma PD (cHMWK) sample[d]	X	X	X	X				X				X				X				X				X		X
Plasma PD (C1-INH and C4) sample[d]	X			X				X				X				X				X				X		X
Plasma antidrug antibody sample[d]	X			X								X								X						X
Lanadelumab administration (6 to <12 years old)	X		X	X		X		X		X		X		X		X		X		X		X		X		X
Lanadelumab administration (2 to <6 years old)	X			X				X				X				X				X				X		
Site check-in call[e]						X				X				X				X				X			X	
Injection report (6 to <12 years old)[f]	X		X	X		X		X		X		X		X		X		X		X		X		X		X
Injection report (2 to <6 years old)[f]	X			X				X				X				X				X				X		

Source: SPRING Trial protocol, table 4, p49-51

Figure 13: Schedule of Activities- Treatment Period B (Week 27 To Week 57) and Follow-up Period

	Treatment Period Shaded columns: scheduled onsite visits Nonshaded columns: potential subject-elected offsite activity																								Follow-up Period			
Study Week	27-28		29-32				33-36				37-40				41-44				45-48				49-52				53-56			
Study Visit (±4 days)	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56 EOS /ET[a]
Study Day	189	196	203	210	217	224	231	238	245	252	259	266	273	280	287	294	301	308	315	322	329	336	343	350	357	364[b]	371	378	385	392
Vital signs[c]		X				X				X				X				X				X				X				X
Physical examination[d]		X				X				X				X				X				X				X				X
Hematology, serum chemistry, and coagulation tests[e]		X								X								X							X				X
Pregnancy testing[f]						X								X								X								X
Plasma PK sample[g]		X								X								X								X				X
Plasma PD (cHMWK) sample[g]		X								X								X								X				X
Plasma PD (C1-INH and C4) sample[g]		X								X								X								X				X
Plasma anti-drug antibody sample[g]		X								X								X								X				X
Lanadelumab administration (6 to <12 years old)		X		X[h]		X		X[h]		X		X[h]		X		X[h]		X		X[h]		X		X[h]		X				
Lanadelumab administration (2 to <6 years old)		X				X				X				X				X				X				X				
Site check-in[i]	X			X				X				X				X				X				X				X[j]		
Injection report (6 to <12 years old)[k]		X		X[h]		X		X[h]		X		X[h]		X		X[h]		X		X[h]		X		X[h]		X				
Injection report (2 to <6 years old)[k]		X				X				X				X				X				X				X				
SC administration survey[l]														X												X				
PedsQL Generic Core Scale[m]		X				X				X				X				X				X				X				X
PedsQL-FIM[m]																										X				X
EQ-5D-Y[m]	Within 24 hours after the onset of symptoms of an HAE attack, if applicable[m]																									X				X
HAE attack data (subject HAE attack diary and site monitoring)[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies, medications, procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EOS visit[o]																														X

AE=adverse event; C1-INH=C1 esterase inhibitor; C4=complement 4; cHMWK=cleaved high molecular weight kininogen; EOS=End of Study; EQ-5D-Y=Youth version of EQ-5D; ET=Early Termination; HAE=hereditary angioedema; PD=pharmacodynamic(s); PedsQL=Pediatric Quality of Life Inventory; PedsQL-FIM=Pediatric Quality of Life Inventory-Family Impact Module; PK=pharmacokinetic(s); SAE=serious adverse event; SC=subcutaneous

[a] The EOS visit on Study Day 392 (Visit 56) occurred only for subjects receiving treatment every 4 weeks; the EOS visit for subjects receiving treatment every 2 weeks occurred on Study Day 378 (Visit 54) (Section 8.1.4 of the study protocol [Appendix 16.1.1])

[b] End of Treatment (Section 8.1.3.3 of the study protocol [Appendix 16.1.1]) was to occur on Day 364/Visit 52 for subjects who completed Treatment Period B. Subjects who prematurely discontinued study treatment should have completed the EOS/ET visit procedures at Day 392/Visit 56, whenever feasible (Section 8.1.4 of the protocol [Appendix 16.1.1]).

[c] Vital signs, including sitting or supine blood pressure, heart rate, body temperature, and respiratory rate were to be measured using standard methods at each study site. On dosing days, vital signs were to be obtained prior (within 60 minutes) to the injection of lanadelumab and 30 minutes (±15 minutes) after completion of the injection of lanadelumab. Additional vital signs measurements were to be performed if clinically indicated.

[d] Complete physical examination, including body weight. Additional physical examination was to be targeted based on reporting of AEs; symptom-oriented physical examinations other than protocol-specified examinations were to be performed when clinically indicated in accordance with standard at the site.

[e] Clinical laboratory testing including hematology, serum chemistry, and coagulation.

[f] Pregnancy testing was to be performed on females who have reached menarche. Tests performed at the indicated visits may have been serum or urine-based.

[g] Blood samples for testing PK, PD, and formation of antibodies to lanadelumab were to be obtained at predose. Note: The EOS PK and PD sample may have been collected at any time of the day. All sample collection and dosing time should have been accurately recorded in the electronic case report form (as date, hours, and minutes). Residual aliquots of blood samples collected for PK, PD, and immunogenicity assessments may have been analyzed for exploratory biomarkers of angioedema disease-state activity.

[h] An individual subject's dose frequency may be modified based on a benefit-risk assessment and recommendation from the treating physician. Consultation with and approval by the sponsor's medical monitor is 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.

[i] If a subject does not have a scheduled onsite visit on the indicated study day, site personnel will perform a site check-in (within 3 days of the study day) to collect AEs and concomitant medications, ensure all HAE attacks have been appropriately documented and, if applicable, ensure that self-administration of lanadelumab (by the subject [aged 6 years or older] or parent/caregiver) has occurred as scheduled. The preferred method of site check-in is a telephone call; however, an alternate method of contact may be considered as site policies permit.

[j] For subjects receiving treatment q4wks only.

Source: SPRING Trial protocol, table 5, p52-54

8.1.1.3.2. Trial Population

The study population included pediatric subjects aged 2 to < 12 years of age with a confirmed diagnosis of type I and II HAE and a minimum baseline attack rate of 1 investigator-confirmed attack per 4-12 weeks during the observation period.

Key inclusion criteria:

- Children (male or female) 2 to < 12 years of age at screening
- Type I or II HAE based on:
  - Documented clinical history consistent with HAE and
  - C1-INH function level <40% of normal or C1-INH level 40-50% of normal with low C4 and
  - At least 1 investigator-confirmed HAE attack per 4-12 weeks during observation period.

Key exclusion criteria:

- Diagnosis of another form of chronic angioedema (e.g., acquired angioedema, type III HAE, idiopathic angioedema, chronic angioedema with urticaria).
- Participation in prior DX-2930 (lanadelumab) study within 4 weeks prior to screening.
- Angiotensin-converting enzyme (ACE) inhibitor or estrogen containing medication within 4 weeks prior to screening.
- Long-term HAE prophylaxis (e.g., C1-INH, androgens, anti-fibrinolytics) within 2 weeks prior to entering the observation period.
- Liver function test abnormalities: alanine transaminase (ALT) or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) or total bilirubin >2x ULN (except for bilirubin elevation due to Gilbert's syndrome).

- Hypersensitivity to the investigational product or its components.
- Pregnancy or breastfeeding.

Subject removal criteria:

Subjects who prematurely discontinued lanadelumab, regardless of the reason, had to undergo the end of study (EOS) visit procedures specified for Day 392 (Visit 56) whenever possible. The reason for lanadelumab discontinuation, and the total amount of lanadelumab administrated had to be recorded in the source documents.

8.1.1.3.3. Treatment

- Lanadelumab 150 mg SC every 2 weeks for subjects 6 to <12 years old; total of 27 doses administrated over the 52-week treatment period. Subjects 6 to <12 years of age could switch to a dosing regimen of 150 mg every 4 weeks in Treatment Period B at the investigator's discretion and Applicant's medical monitor approval, if they were well controlled (e.g., attack-free) for 26 weeks with lanadelumab treatment in this study.
- 150 mg every 4 weeks for subjects 2 to <6 years old; total of 14 doses administered over 52-week treatment period.

Concomitant medications:

Allowed: therapies for co-existing conditions, treatment for acute HAE attacks (including C1-INH for acute attack therapy, but not for long term prophylaxis), treatment for short-term HAE prophylaxis, therapies to treat any adverse events (AEs)

Prohibited: long-term prophylaxis for HAE (e.g., C1-INH, androgens, anti-fibrinolytics), ACE inhibitors, estrogen containing medications with systemic absorption, androgens, any other investigational drug, or device.

8.1.1.3.4. Study Endpoints

Primary Endpoints:

- Safety Endpoints: Adverse events, serious AEs (SsAEs), and AEs of special interest (AESIs). Clinical laboratory testing (hematology, clinical chemistry, and coagulation)
- PK endpoints: C_{max}, C_{avg}, T_{max}, AUC_{tau}, $T_{1/2}$, apparent clearance (CL/F, V/F

Reviewer Note: During the study, all HAE attacks (both SAEs and non-serious AEs), the principal investigator or physician designee reviewed the event and evaluated if it represented a confirmed HAE attack. Any subject-reported attack not confirmed by the investigator was to have an alternate AE diagnosis recorded.

Secondary Endpoints

- Primary Clinical Endpoints: normalized number of investigator-confirmed HAE attacks for the overall treatment period.

- Other clinical outcome endpoints were:
  - Normalized number of investigator-confirmed HAE attacks for each efficacy evaluation period other than the overall treatment period.
  - Time to the first attack, i.e., 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.

8.1.1.3.5. Efficacy Measurements

8.1.1.3.5.1. Collection of Hereditary Angioedema Attacks

Hereditary angioedema attack information was solicited by site personnel during scheduled study visits and site check-ins. Since all study subjects were <18 years of age, parent/caregivers were instructed to report details of the HAE attack to the study site within 72 hours of the onset of the attack.

The collection, reporting, and assessment of HAE attacks was be done in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP) which is a document that provided a definition of an HAE attack, as well as standardized set of procedures for the reporting and assessment of events reported by subjects to help the investigator or physician designee to determine whether those events were confirmed HAE attacks.

Hereditary angioedema attacks were also captured as AEs in the study. A high-morbidity HAE attack was defined as any attack that has at least one of the following characteristics: severe, results in hospitalization (except hospitalization for observation <24 hours), hemodynamically significant (systolic blood pressure <90, requires IV hydration, or associated with syncope or near-syncope), or laryngeal.

8.1.1.3.6. Safety Assessments

Safety monitoring included recording of treatment emergent adverse events (TEAEs), physical exams, vital signs (temperature, heart rate, blood pressure (BP), respiratory rate(RR)), clinical laboratory tests (hematology, chemistry, liver function tests, coagulation, urinalysis, pregnancy), 12-lead electrocardiogram (ECG), and anti-drug antibodies (ADA) according to the schedule in Figure 12 and Figure 13.

8.1.1.3.7. Quality of Life Assessments

Quality of life data was obtained using a Pediatric Quality of Life Inventory (PedsQL) Generic Core Scale (age-appropriate version based on the subjects age on the date of informed consent:

toddler 2-4 years old, young child 5-7 years old, or child 8-12 years old), the PedsQL- Family Impact module (FIM), and the EuroQoL 5-Dimension (EQ-5D-Y) questionnaire for pediatric subjects during scheduled assessments (baseline, visit 26 and 56). In addition to scheduled assessments, the EQ-5D-Y was to be obtained within 24 hours after the onset of symptoms of an HAE attack.

Although the Applicant showed numerically favorable results, these assessments have not been reviewed by Clinical Outcome Assessment Team.

8.1.1.3.8. Statistical Analysis Plan

The clinical development program of lanadelumab for pediatric HAE prophylaxis in children aged 2 to 11 years consisted of a single uncontrolled open-label trial (SPRING Study). SPRING Trial was a PK/PD study conducted as part of an extrapolation strategy to support the use of lanadelumab in this age group and indication. Assessment of safety and PK/PD were the primary endpoints of the study; statistical analysis plan and analysis results regarding the PK/PD endpoints were reviewed under the Clinical Pharmacology review in Section 6 and will not be repeated here. This study also assessed clinical outcome measures (PedsQL, PedsQL-FIM and EQ-5D) and C1-INH and C4 as exploratory clinical/PD endpoints.

With the small sample size and uncontrolled design, DX-2903-04 provided limited clinical outcome measure data and was not designed to detect significant changes in the clinical assessments. All clinical outcome analyses were based on the safety set, which was defined as all subjects who received any dose of lanadelumab. Only descriptive analyses were conducted.

This section will describe aspects of the statistical analysis plan (SAP) on sample size determination, analysis population, and summary statistics used for selected primary endpoints, based primarily on the Applicant's methodologies and analysis of the results.

Sample Size

No formal sample size calculation was performed. The sample size is not based on any statistical considerations. This study is designed to evaluate the safety and efficacy of open-label treatment with DX-2930.

Analysis Populations

The Safety Population included all subjects who received any study drug (i.e., any exposure to open-label DX-2930).

All data listings were sorted by long-term prophylaxis therapy, site, and subject number, and included the subject's age, sex, and race.

Analysis of Efficacy

The Safety Population consisted of all subjects who received any lanadelumab.

Primary Efficacy Analysis: The primary objective for this study was safety. All other efficacy endpoints were secondary.

Secondary Endpoints:

- Normalized (per 4 weeks during Treatment Period) number of investigator-confirmed HAE attacks for the overall treatment period. (Key secondary endpoint, described by the Applicant as the primary clinical outcome endpoint.) Note: The normalized number of investigator-confirmed HAE attacks during each efficacy evaluation period was expressed as a monthly HAE attack rate. The baseline investigator-confirmed HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the baseline observation period divided by the number of days the subject contributed to the observation period multiplied by 28 days.
- Normalized number of investigator-confirmed HAE attacks for each efficacy evaluation period other than the overall treatment period.
- Time to the first attack, i.e., duration that a subject is 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.
- Achievement of attack-free status for each efficacy evaluation period.

The estimand for the key secondary endpoint, as defined by the Applicant, was:

Target Population: Pediatric patients (aged 2 to <6, 6 to <12 and overall) with HAE

Intercurrent events:

- IMP-related Discontinuation: While on treatment strategy: Count attacks through end of Treatment Period B
- IMP-unrelated Discontinuation: While on treatment strategy: Count attacks through end of Treatment Period B
- IMP Interruption: Treatment policy strategy, ignoring the interruption
- Medications: Treatment policy strategy, attacks are included regardless of the use of other medications

Summary measure: Normalized number of investigator-confirmed HAE attacks per 4 weeks during Treatment Period and comparison to normalized number of investigator-confirmed HAE attacks per 4 weeks during baseline observation period.

Analyses on continuous clinical outcome endpoints (e.g., HAE attack rates) were analyzed using descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum (min), and maximum (max). Categorical clinical outcome endpoints (e.g., attack severity) were summarized by the number of subjects in each category and the percentage of subjects out of the total in the respective analysis set. Time-to-event endpoints (e.g., time to the first HAE attack) were analyzed using Kaplan-Meier (KM) estimates. Summaries included median time and quartiles, if estimable, and corresponding 95% confidence intervals.

8.1.1.3.9. Compliance With Good Clinical Practices

A statement of compliance with Good Clinical Practice is in the Clinical Study Report.

8.1.1.3.10. Financial Disclosure

The Applicant has adequately disclosed financial interests and arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators (see **Appendix 15.2**).

8.1.1.4. Study Results

8.1.1.4.1. Protocol Amendments

The original clinical study report was approved on March 25, 2022. On May 23, 2022, after the finalization of the clinical study report, it was found that the algorithm created to derive the patient-years values for the dose regimens was not accurate for the overall study period and the overall treatment period. Specifically, for subjects who switched from q2wks to q4wks dosing and vice versa, the algorithm used the total amount of time that a subject was on the overall treatment period or the overall study period rather than the total time that a subject was on a particular dosing regimen.

The update to the algorithm used to derive the patient-years values resulted in changes in the total patient-year exposure and the adverse event rate per patient-year by dosing regimen during the overall treatment period, overall study period, and the follow-up period.

8.1.1.4.2. Protocol Deviations

Protocol deviations were collected at both the site and subject level. Deviations at the site level were applied to all subjects who were enrolled at that site at the time of the deviation. Three subjects had deviations related to the inclusion criteria. Twelve subjects had deviations related to COVID-19, of which 2 (10%) subjects experienced study disruptions. Both subjects were in the q2wks group and had 1 disruption each (1 subject missed visit 2 [day 4] and the other subjects missed Visit 52 [Day 364]). Other minor protocol deviations occurred related to the timing of blood sample collection.

8.1.1.4.3. Efficacy

8.1.1.4.3.1. Patient Disposition

A total of 24 subjects were screened, 21 subjects qualified and were enrolled. All enrolled subjects received at least one dose of lanadelumab.

A total of 20 (95%) subjects completed Treatment Period A and Period B. One subject who was receiving lanadelumab 150mg q4wks discontinued the study prematurely due to withdrawal by the parent/guardian prior to the completion of Treatment Period A.

During Treatment Period B, 7 subjects switched from q2wks to q4wks dosing after being attack free during Treatment Period A. One subject (5-year-old) switched from q4wks to q2wks dosing during Treatment Period B due the presence of moderate to severe attacks and because he was eligible for q2w dosing as he turned 6 years of age (See Section 8.1.2 for additional details).

Figure 14. Subject Disposition by Treatment Group

	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.

Source: SPRING Trial protocol, Table 7, p84.

8.1.1.4.3.2. Demographics

The demographics are summarized in Table 9. Majority of subjects were female (57%) and white (95%). The mean age was 7.5 years old. A total of 13 subjects were enrolled in the 2 to < 9-year age group and 8 in the 9 to < 12-year age group. Most subjects were from the United States (62%), and Europe (29%), with a smaller percentage from Canada (10%).

Table 9. Demographic Characteristics

Characteristic	Lanadelumab 150 mg every 4 weeks (N=4)	Lanadelumab 150 mg every 2 weeks (N=17)	Total (N=21)
Sex			
Female	2 50.0	10 58.8	12 57.1
Male	2 50.0	7 41.2	9 42.9
Age			
Mean (SD)	4.2 0.96	8.3 1.26	7.5 (2.02)
Median (min, max)	4.5 (3, 5)	8.0 6, 10	8.0 (3, 10)
Age group			
2 to <9 years	4 100.0	9 52.9	13 61.9
9 to <12 years	0	8 47.1	8 38.1
Race			
Asian	0	1 (5.9	1 (4.8
White	4 100.0	16 94.1	20 95.2
Ethnicity			
Hispanic or Latino	0	2 11.8	2 (9.5
Not Hispanic or Latino	4 100.0	15 88.2	19 90.5
Region			
Canada	1 25.0	1 (5.9	2 (9.5
Europe	2 50.0	4 23.5	6 28.6
U.S.	1 25.0	12 70.6	13 61.9

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Sex - Dataset: Demographics; Filter: None.
Age - Dataset: Demographics; Filter: None.
Age Group - Dataset: Demographics; Filter: None.
Race - Dataset: Demographics; Filter: None.
Ethnicity - Dataset: Demographics; Filter: None.
Region - Dataset: Demographics; Filter: None.
Abbreviations: Min: minimum; Max: maximum; N: total number; SD: Standard Deviation; U.S.: United States

Reviewer Comments: All ethnicities and races are affected by types I and II HAE; however, most of the epidemiologic and genetic data that exists is derived from European populations. The interaction between race and disease expression is poorly understood. Although there is just one non-white patient in this study, this is understandable with a rare disease.

8.1.1.4.3.3. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Baseline disease characteristics were generally similar across treatment arms (Table 10). Most patients have type I HAE, which reflects the reported epidemiology. The majority of subjects did not previously receive long-term prophylactic treatments. Thirteen patients (62%) reported abdominal attacks as their primary attack location, followed by peripheral attacks in 7 patients (33%). The majority of the reported attacks were moderate in severity. Treatment compliance was high in this group. All patients received at least 80% of planned doses.

Table 10. Baseline HAE Attack History

Characteristics	Lanadelumab 150 mg every 4 weeks (N=4)	Lanadelumab 150 mg every 2 weeks (N=17)	Total (N=21)
Weight (kg)			
Mean (SD	20.4 (3.24)	34.7 (12.48)	32.0 12.63
Median (min, max)	21 (15.8,23.5)	31.05 19.6,63.3	29.93 15.8,63.3
BMI kg/m2			
Mean (SD)	16.5 1.43	18.9 (4.44)	18.4 (4.12)
Median (min, max)	16.23 15.3,18.2	17.83 (14.1,30.5)	17.56 14.1,30.5
Age on onset of angioedema symptoms (years)			
Mean (SD	2.0 (1.41)	3.5 (2.85)	3.2 2.68
Median (min, max)	1.5 (1, 4)	3.0 (0, 9)	2.0 (0, 9)
HAE type - n (%)			
Type I	4 100.0	16 94.1	20 95.2
Unspecified-type I or type II	0	1 5.9	1 4.8
Type of LTP - n (%)			
C1-INH	1 (25)	2 (11.8)	3 (14.3)
Oral therapy	0	0	0
C1-INH and oral therapy	0	0	0
Not on LTP	3 (75)	15 (88.2)	18 (85.7)
History of laryngeal attacks - n (%)			
No	3 75.0	13 76.5	16 76.2
Yes	1 25.0	4 23.5	5 23.8
Primary attack locations - n (%)			
Abdominal	2 50.0	11 64.7	13 61.9
Laryngeal	0	1 (5.9	1 (4.8
Peripheral	2 50.0	5 29.4	7 33.3
Primary attack locations (combined) n (%)			
Abdominal	2 50.0	11 64.7	13 61.9
Laryngeal	0	1 (5.9	1 (4.8
Peripheral	2 50.0	5 29.4	7 33.3
Historical number of attacks in the last month			
Mean (SD)	2.8 2.06	1.9 (2.25)	2.1 (2.19)
Median (min, max)	3.0 (0, 5)	1.0 (0, 8)	1.0 (0, 8)
Historical number of attacks in the last 3 months			
Mean (SD)	4.8 (4.35)	4.3 (3.08)	4.4 (3.23)
Median (min, max)	3.5 (1, 11)	4.0 (0, 13)	4.0 (0, 13)
Historical number of attacks in the last 12 months			
Mean (SD)	17.0 (24.01)	15.2 12.64	15.5 14.66
Median (min, max)	5.5 (4, 53)	15.0 1, 56	12.0 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
Number of mild HAE attacks in the last 3 months			
Mean (SD)	3.5 (3.11)	1.2 (1.33)	1.6 1.94
Median (min, max)	2.5 (1, 8)	1.0 (0, 4)	1.0 (0, 8)

Characteristics	Lanadelumab 150 mg every 4 weeks (N=4)	Lanadelumab 150 mg every 2 weeks (N=17)	Total (N=21)
Number of moderate HAE attacks in the last 3 months			
Mean (SD)	1.0 (1.41)	2.4 (2.40)	2.1 (2.29)
Median (min, max)	0.5 (0, 3)	2.0 (0, 8)	2.0 (0, 8)
Number of severe HAE attacks in the last 3 months			
Mean (SD)	0.2 (0.50)	0.7 (0.99)	0.6 0.92
Median (min, max)	0.0 (0, 1)	0.0 (0, 3)	0.0 (0, 3)
Total number of doses received			
N	11	18	21
Mean (SD)	7.5(3.5)	21.3 6.5	22.1 6.27
Median (min, max)	7 (2,14)	26.5 13,27	22 (2,27)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Age on Onset of Angioedema Symptoms (years) - Dataset: Demographics; Filter: None.
HAE Type - n(%) - Dataset: Demographics; Filter: None.
History of Laryngeal Attacks - n(%) - Dataset: Demographics; Filter: None.
Primary Attack Locations - n(%) - Dataset: Demographics; Filter: None.
Primary Attack Locations (Combined) n(%) - Dataset: Demographics; Filter: None.
Historical Number of Attacks in the Last Month - Dataset: Demographics; Filter: None.
Historical Number of Attacks in the Last 3 Months - Dataset: Demographics; Filter: None.
Historical Number of Attacks in the Last 12 Months - Dataset: Demographics; Filter: None.
Average Severity of HAE Attacks in the Last 12 Months - n(%) - Dataset: Demographics; Filter: None.
Number of Mild HAE Attacks in the Last 3 Months - Dataset: Demographics; Filter: None.
Number of Moderate HAE Attacks in the Last 3 Months - Dataset: Demographics; Filter: None.
Number of Severe HAE Attacks in the Last 3 Months - Dataset: Demographics; Filter: None.
Abbreviations: BMI: body mass index ; C1-INH: C1 esterase inhibitor; HAE: hereditary angioedema; Kg: kilogram; LTP: long-term prophylaxis; SD: standard deviation; mg: milligrams; Min: minimum; Max: maximum; N: total number

8.1.1.4.3.4. Primary Endpoint

Safety and PK were the primary endpoints. The PK results were discussed in the Clinical pharmacology Section 6. Safety endpoints are reviewed in Section 8.2.

8.1.1.4.3.5. Secondary Endpoints

PD assessments and immunogenicity endpoints results are discussed in the Clinical Pharmacology Section 6. Clinical outcome measurements were secondary endpoints for the study. The primary clinical outcome endpoint was the normalized number of investigator-confirmed HAE attacks for the overall treatment period.

For efficacy analyses subjects were analyzed based on the actual treatment received. Overall, the mean (SD) and median rate of investigator-confirmed HAE attacks decreased from 1.84 (1.53) and 1.44 attacks/month during the baseline observation period to 0.08 (0.17) and 0.00 attacks/month at the end of the overall treatment period; (N=21). Results were similar in both the q4wks group (from 1.45 [0.79] and 1.12 attacks/months to 0.07 [0.22] and 0.00 attacks/month; N=11) and the q2wks group (from 1.91 [1.63] and 1.28 attacks/month to 0.08 [0.16] and 0.00 attacks/month; N=18).

8.1.2. Assessment of Efficacy Across Trials

Efficacy for pediatric subjects 2 to <12 years of age (SPRING Trial) is based on extrapolation for adults and adolescents (HELP Study). The extrapolation was supported by PK analysis showing similar drug exposure levels for 150 mg administrated subcutaneously every 2-4 weeks and a similar PD response. Extrapolation of efficacy based on comparable systemic exposure is appropriate because of the similar clinical presentation of both adult and pediatric HAE, consistency in therapeutic approach, consistency of lanadelumab mechanism of actions, and relevance of the clinical endpoints for both efficacy and safety.

SPRING Trial was not designed to assess efficacy given the small sample size, and uncontrolled design. However, exploratory efficacy analysis demonstrated results consistent with the adolescent and adult trials (See Table 11).

Table 11. Comparison of Efficacy Measures (SPRING Study < 12 Years of Age vs. HELP Study ≥12 Years of Age)

	TAKHZYRO					
	SPRING Trial <12yo		HELP Study ≥12yo			
Criteria	150 mg q4wks	150 mg q2wks	Placebo	150 mg q4wks	300 mg q4wks	300 mg q2wks
N	4	17	41	28	29	27
Attack rate reduction from baseline (attacks/month) Mean (SD)	1.71 (0.77)	1.75 1.63	1.57 (3.87)	2.73 (1.93)	3.11 2.63	3.21 (2.38)
% Attack rate reduction from baseline Mean (SD or 95% CI)	95 (9.45)	93 (22.98)	39 (25.0)	85 (17.8)	83 (18.4)	91 (18.8)
Number of attack-free subjects n (%)	3 (75.0)	14 (82.4)	1 (2.4)	11 (39.3)	9 (31.0)	12 (44.4)
% Attack free days; mean (SD)	99.3 (1.4)	99.6 1.0	81 16	96 6	96 5	98 (5)

Sources: HELP clinical study report (CSR) Table 14.2.2.1 for number of HAE attack rate reduction and % attack rate reduction*Table 14.2.14.1 for attack-free days
Table 14.2.15.1 for attack-free subjects
* Mean and SD calculated by statistical reviewer from descriptive mean/SD for treatment and run-in periods
Abbreviations: N: total number; q2wks: every 2 weeks; q4wk: every 4 weeks

Overall, 7 subjects aged 6 to < 12 years switched from q2wks during Treatment Period A to q4wks dosing for Treatment Period B. In addition, during Treatment Period B, a 5 year old subject who was enrolled in Treatment Period A at 150 mg q4w based on his age, switched from q4wks to q2wks dosing as he turned 6 years of age at the time of Treatment Period B and

had a high rate of attacks during Treatment Period A (2.8 attacks/month). After switching to q2w dosing his attack rate decreased from 2.8 attacks/month to 0.2 attacks/month.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review is divided into the two study periods: Period A and Period B. Period A consisted of a 26-week treatment period and Period B was a 26-week treatment period and 2 to 4 weeks follow-up phase. Adverse events were monitored during the entirety of the study. The safety data for the two parts were not pooled and will be reviewed individually.

8.2.2. Review of the Safety Database

Overall Exposure

Subjects who received lanadelumab every 2 weeks, received a total of 27 doses over the 52-week treatment period. Subjects receiving lanadelumab every 4 weeks, received a total of 14 doses administrated over 52-week period. All subjects received at least 80% of the planned doses.

Adequacy of the Safety Database

Overall, the safety database is of sufficient size and duration to assess the safety of the proposed pediatric dose given the previous safety database for the approved adolescent and adult asthma indication.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data integrity or submission quality issues that hinder the safety review of this sBLA were identified.

Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events and serious events in the protocols. Adverse events (AEs) were captured from signing of informed consent through the final follow up visit. This included events occurring during the screening phase, regardless of whether the investigational product had been administered. Treatment emergent adverse events (TEAE) were defined as any AEs were defined as AEs with onset at the time of or following the first exposure to lanadelumab in this study or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. AE were classified into system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0.

The Applicant's coding of verbatim terms to preferred terms was appropriate. Adverse events

of special interest included hypersensitivity reactions and disorders in coagulation (hypercoagulability events and bleeding events).

8.2.4. Safety Results

Deaths

There were no deaths in either Period A or Period B of the study.

Serious Adverse Events

There were no SAEs reported during the study.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no study discontinuations or dropouts due to AEs during Period A or Period B.

Treatment Emergent Adverse Events and Adverse Reactions

Given the absence of a placebo group in SPRING Trial, it is difficult to assess relatedness of events to medication use. Generally, events were mostly singular and balanced between treatment arms. A review of all AEs in SPRING Trial did not reveal any new safety concerns. Common AEs (occurring in ≥ 2 subjects by system organ class and treatment group) reported are summarized in Table 12, Table 13, Table 14. In both Period A and Period B injection site pain and infections were common AEs seen. Overall, the common adverse events for pediatric patients are similar to that observed in patients aged 12 years and older which included of injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea.

Table 12. Treatment Period A: Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events in ≥ 2 Subjects by System Organ Class, Preferred Term, and Treatment Group (Safety Set)

System Organ Class - Preferred Term	Lanadelumab 150 mg every 4 weeks N=4 n (%)	Lanadelumab 150 mg every 2 weeks N=17 n (%)	Total N=21 n (%)
Gastrointestinal disorders	0 (0.0)	2 (11.8)	2 (9.5)
General disorders and administration site conditions	2 (50.0)	6 35.3	8 (38.1)
Injection site erythema	1 (25.0)	2 (11.8)	3 (14.3)
Injection site pain	1 (25.0)	5 (29.4)	6 28.6
Pyrexia	0 (0.0)	2 (11.8)	2 (9.5)
Infections and infestations	1 (25.0)	8 (47.1)	9 (42.9)
Nasopharyngitis	1 (25.0)	1 (5.9)	2 (9.5)
Upper respiratory tract infection	0 (0.0)	2 (11.8)	2 (9.5)
Injury, poisoning and procedural complications	1 (25.0)	3 17.6	4 (19.0)
Nervous system disorders	0 (0.0)	2 (11.8)	2 (9.5)
Headache	0 (0.0)	2 (11.8)	2 (9.5)

System Organ Class - Preferred Term	Lanadelumab 150 mg every 4 weeks N=4 n (%)	Lanadelumab 150 mg every 2 weeks N=17 n (%)	Total N=21 n (%)
Respiratory, thoracic, and mediastinal disorders	2 (50.0)	1 (5.9)	3 (14.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Lanadelumab 150 mg every 4 weeks" and SAFFL = "Y" (Lanadelumab 150 mg every 4 weeks); TRT01A = "Lanadelumab 150 mg every 2 weeks" and SAFFL = "Y" (Lanadelumab 150 mg every 2 weeks); TRT01A = "Lanadelumab 150 mg every 2 weeks" or "Lanadelumab 150 mg every 4 weeks" and SAFFL = "Y" (Total); TRTEMFL = "Y" and APERIODC = "Treatment Period A" and AEBODSYS <> "Congenital, familial and genetic disorders" Adverse Events). Percent Threshold: Total ≥ 5%
Abbreviation: HAE: hereditary angioedema; N: total number

Table 13. Treatment Period B: Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events in ≥ 2 Subjects by System Organ Class, Preferred Term, and Treatment Group (Safety Set)

System Organ Class - Preferred Term	Lanadelumab 150 mg every 4 weeks N=10* n(%)	Lanadelumab 150 mg every 2 weeks N=18* n(%)	Total N=20 n(%)**
Gastrointestinal disorders	1(10.0)	3 16.7	3(15.0)
Abdominal pain	1(10.0)	2(11.1)	2(10.0)
General disorders and administration site conditions	1(10.0)	3 16.7	4(20.0)
Injection site pain	1(10.0)	3 16.7	4(20.0)
Infections and infestations	2(20.0)	2(11.1)	4(20.0)
Injury, poisoning and procedural complications	2(20.0)	3 16.7	5(25.0)
Skin abrasion	1(10.0)	2(11.1)	3(15.0)
Musculoskeletal and connective tissue disorders	0(0.0)	2(11.1)	2(10.0)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0(0.0)	3 16.7	3(15.0)
Skin papilloma	0(0.0)	3 16.7	3(15.0)
Respiratory, thoracic, and mediastinal disorders	2(20.0)	2(11.1)	4(20.0)
Skin and subcutaneous tissue disorders	1(10.0)	1 5.6	2(10.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "Lanadelumab 150 mg every 4 weeks" and COMPLBFL = "Y" and SAFFL = "Y" (Lanadelumab 150 mg every 4 weeks); TRTNEW = "Lanadelumab 150 mg every 2 weeks" and COMPLBFL = "Y" and SAFFL = "Y" (Lanadelumab 150 mg every 2 weeks); TRTNEW = "Lanadelumab 150 mg every 2 weeks" or "Lanadelumab 150 mg every 4 weeks" and SAFFL = "Y" (Total); TRTEMFL "Y" and AESOC <> "Congenital, familial and genetic disorders" Adverse Events).
Percent Threshold: Total ≥ 10%.
* Number of subjects who reported an AE in each cohort (a subject can report the same event in the different dose regimens); N= 10 includes the initial 4 subjects + the 7 subjects who switched from q2wks to q4wks minus the one subject who switched from q4wks to q2wks (USUBJID (b) (6)); N=18 includes the initial 17 subjects included + the subject (USUBJID (b) (6)) who switched from q4wks to q2wks due to increase HAE attacks and also due to age patient just turned 6 at the time of dose adjustment)
** Total column only captures the total number of unique subjects who reported an AE during one or both treatment periods.
Abbreviations: AE: adverse events; HAE: hereditary angioedema; N= total number.

Table 14. Overall Treatment Period: Treatment Emergent Adverse Events (Excluding HAE Attack Reported Events in ≥ 2 Subjects by System Organ Class, Preferred Term, and Treatment Group (Safety Set)

System Organ Class - Preferred Term	Lanadelumab 150 mg every 4 weeks N=11* n (%)	Lanadelumab 150 mg every 2 weeks N = 18* n (%)	Total N = 21 n (%)**
Eye disorders	0 (0.0)	2 (11.1)	2 (9.5)
Gastrointestinal disorders	1 (9.1)	5 (27.8)	5 (23.8)
Abdominal pain	1 (9.1)	2 (11.1)	2 (9.5)
General disorders and administration site conditions	3 (27.3)	7 (38.9)	8 (38.1)
Injection site erythema	2 (18.2)	2 (11.1)	3 (14.3)
Injection site pain	2 (18.2)	6 33.3	6 28.6
Pyrexia	0 (0.0)	2 (11.1)	2 (9.5)
Infections and infestations	3 (27.3)	10 55.6	11 (52.4)
Nasopharyngitis	1 (9.1)	2 (11.1)	2 (9.5)
Upper respiratory tract infection	0 (0.0)	2 (11.1)	2 (9.5)
Injury, poisoning and procedural complications	3 (27.3)	5 (27.8)	6 28.6
Joint injury	2 (18.2)	0 (0.0)	2 (9.5)
Skin abrasion	1 (9.1)	3 16.7	3 (14.3)
Musculoskeletal and connective tissue disorders	0 (0.0)	3 16.7	3 (14.3)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0 (0.0)	3 16.7	3 (14.3)
Skin papilloma	0 (0.0)	3 16.7	3 (14.3)
Nervous system disorders	1 (9.1)	2 (11.1)	3 (14.3)
Headache	1 (9.1)	2 (11.1)	3 (14.3)
Respiratory, thoracic, and mediastinal disorders	3 (27.3)	3 16.7	5 (23.8)
Nasal congestion	2 (18.2)	0 (0.0)	2 (9.5)
Skin and subcutaneous tissue disorders	1 (9.1)	2 (11.1)	2 (9.5)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTNEW = "Lanadelumab 150 mg every 4 weeks" and SAFFL = "Y" (Lanadelumab 150 mg every 4 weeks); TRTNEW = "Lanadelumab 150 mg every 2 weeks" and SAFFL = "Y" (Lanadelumab 150 mg every 2 weeks); TRTEMFL = "Y" and AESOC <> "Congenital, familial and genetic disorders" (Adverse Events).
Percent Threshold: Total Column ≥ 5%.
* Number of subjects who reported an AE in each cohort (a subject can report the same event in the different dose regimens); N= 11 includes the initial 4 subjects included + the 7 subjects who switched from q2wks to q4wks; N=18 includes the initial 17 subjects included + the subject (USUBJID (b) (6)) who switched from q4wks to q2wks due to increase HAE attacks and also due to age (patient just turned 6 at the time of dose adjustment)
** Total column only captures the total number of unique subjects who reported an AE during one or both treatment periods.
Abbreviations: AE: adverse events; HAE: hereditary angioedema; N: total number

Laboratory Findings

Laboratory assessments (hematology, chemistry, and urinalysis) were conducted periodically during the study. All chemistry results were compared with baseline. The majority of subjects had values for clinical chemistry within normal range. Given that patients aged 12 years and older had some cases of transaminitis in the HELP study, this was monitor closely on this cohort. There was no abnormal liver function test reported during this study.

Vital Signs

Routine vital signs (sitting pulse rate, respiratory rate, blood pressure, and temperature) were performed periodically during the study. The mean changes from baseline in all parameters were small and there were no treatment effects detected. In total, 3 TEAEs related to vital sign abnormalities were reported during the study; 2 subjects in the q2wks group had 1 event of pyrexia each, and 1 subject in the q2wks had one event of feeling cold.

Immunogenicity

No subjects reported positive ADA results at baseline. For the overall treatment period, 3 (15%) subjects were ADA positive; all of which were in the q2wks group (3 [15%] subjects in Treatment Period A and 1 [5%] subject in Treatment Period B). Of these, 1 (33%) subject had neutralizing antibodies. The occurrence of ADAs and neutralizing antibodies had no impact on clinical outcomes, PK, PD, or safety of lanadelumab.

8.2.5. Analysis of Submission-Specific Safety Issues

Analysis of Submission-Specific Safety Issues

Hypersensitivity reactions and transaminase elevations emerged as a potential safety signal based on the original BLA (HELP trial). Although abnormal bleeding/hypercoagulability events were identified as adverse events of special interest (AESIs) a priori based on knockout animal models, no events were reported. Due to this, the SPRING trial considered adverse events of special interest (AESIs) hypersensitivity reactions and coagulation disorders (hypercoagulability events and bleeding events). There were no AESIs of hypersensitivity and disordered coagulation (hypercoagulability events and bleeding events) reported by the investigators. The incidence of AESIs was low in this study and all the events were reported in the cohort who was receiving lanadelumab every 2 weeks.

Table 15 SPRING Trial- Overall Number of Subjects With Adverse Events of Special Interest (Excluding HAE Attack Reported Events)

Category	Lanadelumab 150 mg every 4 weeks (N=4) n (%)	Lanadelumab 150 mg every 2 weeks (N=17) n (%)	Total (N=21) n (%)
Hypersensitivity AESIs			
Dermatitis allergic	0	1 (5.8)	1 (4.8)
Eosinophil count increased	0	1 (5.8)	1 (4.8)
Erythema	0	1 (5.8)	1 (4.8)
Pruritus	0	1 (5.8)	1 (4.8)
Seasonal allergy	0	1 (5.8)	1 (4.8)
Urticaria	0	1 (5.8)	1 (4.8)

Category	Lanadelumab 150 mg every 4 weeks (N=4) n (%)	Lanadelumab 150 mg every 2 weeks (N=17) n (%)	Total (N=21) n (%)
Bleeding AESIs			
Contusion	0	1 (5.8)	1 (4.8)
Epistaxis	0	1 (5.8)	1 (4.8)
Hematoma	0	1 (5.8)	1 (4.8)
Thromboembolic AESIs			
Total	0	0	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns-Dataset: demographics; Filter: SAFFL = 'Y'
Hypersensitivity AESIs- Dataset: Adverse Events; Filter: SAFFL = 'Y', HYNSEN = 'Y'
Bleeding AESIs-Dataset: Adverse Events; Filter: TRTEMFL = 'Y', BLEED = 'Y'
Thromboembolic AESIs- Dataset: Adverse Events; Filter: TRTEMFL = 'Y', SAFFL + 'Y'
Abbreviations: AESI: adverse events of special interest; HAE: heredity angioedema

8.2.6. Safety Analyses by Demographic Subgroups

Safety analysis by demographic subgroup was not conducted due to the small study size.

8.2.7. Safety in the Post-market Setting

Safety Concerns Identified Through Post-Market Experience

No new safety concerns have been identified based on post-marketing experience since lanadelumab was approved for patients > 12 years of age in 2018.

8.2.8. Integrated Assessment of Safety

There were no new safety concerns identified in SPRING Trial that alter the risk-benefit profile of lanadelumab for the population 2 to <12 years of age. The frequency and type of AEs were consistent with previous studies in adults and adolescents. There were no deaths, SAEs, or investigator confirmed AESIs reported during the study. No subjects discontinued the study due to TEAEs. The most commonly reported TEAE was injection site pain and most TEAEs were mild or moderate in severity. No clinically meaningful changes in laboratory values were described during this trial.

8.3. Statistical Issues

No statistical issues were identified in this single-arm trial, which was assessed with descriptive statistics and comparisons to baseline and to the adequate and well-controlled adolescent and adult study.

8.4. Conclusions and Recommendations

The recommended regulatory action is approval of lanadelumab for prophylaxis to prevent attacks of HAE in pediatric patients 2 years and < 12 years old. Substantial evidence of effectiveness for lanadelumab to prevent attacks of HAE in children 2 to < 12 years of age is

provided by extrapolation from evidence that supported substantial evidence of effectiveness from the approval of lanadelumab for the same indication in adults and adolescents 12 years of age and older. Efficacy extrapolation for children 2 to < 12 years of age based on the adequate and well-controlled trials conducted in adults and adolescents (≥ 12 years of age) is supported by the similar clinical presentation of both adult and pediatric HAE, consistency in the therapeutic approach, consistency of the lanadelumab mechanism of action, and relevance of the clinical endpoints. Comparable systemic exposure for 150 mg administrated subcutaneously (SC) every 2 weeks (patients aged 6 to <12 years) or every 4 weeks (patients aged 2 to < 6 years) to the approved 300 mg SC dose every 2 weeks, and a similar pharmacodynamic response was demonstrated. Long-term safety in patients 2 to < 12 years of age was evaluated; the safety profile is similar to the established safety profile in adolescents and adults. The overall risk-benefit is favorable for the approval of lanadelumab down to age 2 for prophylaxis to prevent attacks of HAE.

Expanding the availability of lanadelumab to children 2 to < 12 years of age addresses an important unmet need for this rare disease. With the exception of danazol, an androgen with many adverse effects, lanadelumab proposes to be the first prophylactic HAE therapy for children less than 6 years of age. Of the injectable HAE prophylactic therapies, this supplement also introduces the first pre-filled syringe for use in children less than 12 years of age (current products are vials for SC or intravenous use).

9. Advisory Committee Meeting and Other External Consultations

As lanadelumab is approved for the same indication in adolescents and adults and there were no safety or efficacy concerns identified for this pediatric program, no advisory committee meeting was required.

10. Pediatrics

Lanadelumab was granted Orphan Designation for treatment of angioedema on November 26, 2013, for the treatment of angioedema which exempts lanadelumab for HAE from PREA. A WR was issued July 20, 2018 and amended on April 16, 2019. The single trial that supports this sBLA (SPRING) was conducted to fulfil WR Amendment #1. At the Pediatric Exclusivity Board on November 30, 2022 it was determined that the Applicant fulfilled all requirements (including and that Applicant submitted the trial before the September 1, 2023 deadline). Exclusivity was granted on December 20, 2022 (See Pediatric Exclusivity Determination Checklist submitted to BLA 761090 on December 20, 2022) and the Applicant was notified on December 23, 2022. On December 13, 2022, The Pediatric Review Committee (PeRC) was informed of the Pediatric Exclusivity Board's decision for this product.

With this sBLA, the Applicant requested a rare pediatric disease priority voucher. The voucher was denied as a rare pediatric disease priority voucher must be submitted with a rare pediatric disease product application. The term 'rare pediatric disease product application' means a human drug application. Section 735(1) (under Section 529(a)(4) of the FD&C Act) states that the term "human drug application" does not include supplements, therefore this supplement is not a "human drug application" that could be eligible for a priority review voucher under the statute.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Table 16. Labeling Changes

Full Prescribing Information Sections[1]	Rationale for Major Changes Incorporated Into the Finalized Prescribing Information (PI)[2]
1 INDICATIONS AND USAGE	The indication is expanded from adult and pediatric patients *12* years and older to adult and pediatric patients aged *2* years and older.
2 DOSAGE AND ADMINISTRATION	Addition of Recommend Dosages for pediatric patients 6 to less than 12 years of age and for pediatric patients 2 to less than 6 years of age. Revised Preparation and Administration Instructions subsection to include information for administration of TAKHZYRO by patient and/or caregiver according to the patient's age.
6 ADVERSE REACTIONS	Addition of safety information for Pediatric Patients 2 to less than 12 years of age. Relocated Immunogenicity information to subsection 12.6 consistent with Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling (draft guidance). Removed (b) (4) from description of open-label extension trial (Trial 1; DX-2930-04; HELP Trial Extension) which completed in 2019 and fulfilled PMC 3466-1 (see Dr. Clarridge's DARRTs Clinical Review dated June 28, 2021).
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Pediatric Use subsection was revised to reflect the approved patient population and the supporting evidence for the basis of approval.
12 CLINICAL PHARMACOLOGY	Addition to Pharmacodynamics subsection with new information (the observed mean percent change from baseline cHMWK levels) for pediatric patients less than 12 years of age. Updated Pharmacokinetic subsection with new pediatric information for the Pediatric Population. Relocated Immunogenicity information from Section 6 and addition of pediatric immunogenicity information.
13 NONCLINICAL TOXICOLOGY	
14 CLINICAL STUDIES	(b) (4) .
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Addition of new dosage form and strength, 150 mg/mL solution in a single-dose prefilled syringe.

Source: Labeling Discussion Comments dated January 10, 25, and 31, 2023. Final label submitted February 1, 2023.

1 The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
2 For the purposes of this document, the finalized prescr bing information (PI) is the PI that will be approved or is close to being approved. The finalized PI was compared to the FOR NDAs/BLAs: applicant's draft PI (FOR EFFICACY SUPPLEMENTS: currently approved PI and the applicant's draft PI).

12. Risk Evaluation and Mitigation Strategies

Given the favorable safety profile of lanadelumab for 2 to <12 years old, there are no additional risk management strategies required.

13. Post Marketing Requirements and Commitment

None

14. Division Director (Clinical) Comments

Hereditary angioedema (HAE) is a rare, autosomal dominant, potentially life-threatening disorder characterized by unpredictable attacks of angioedema, including laryngeal edema. It is estimated that 50-75% of patients have their first attack by the time they are 12 years of age; HAE attacks during infancy are considered rare. HAE attacks beginning at an early age may be associated with a more severe phenotype of HAE. Prophylaxis to prevent acute attacks of HAE is a central goal of treatment of HAE. At present, only danazol, an androgen, is available for preventive treatment in patients <6 years of age; danazol has a safety profile that may limit its use. For patients 6 to <12 years of age, there are 2 approved preventive treatments consisting of plasma-derived C1 esterase inhibitor (Cinryze and Haegarda), in addition to danazol.

HAE is caused by mutations in the SERPING1 gene, resulting in deficiency or dysfunction of C1-esterase inhibitor (C1-INH) protein, a serine protease inhibitor. Absence of functional C1-INH leads to dysregulation of the contact system, a plasma protease cascade initiated by factor XII (FXII) that activates the proinflammatory kallikrein-kinin system and the procoagulant intrinsic coagulation pathway. Kallikrein activity is regulated by C1-INH, but in HAE patients kallikrein activity goes unchecked, leading to widespread release of bradykinin. In turn, bradykinin increases vascular permeability which leads to the characteristic swelling of acute HAE attacks.

Lanadelumab is a fully human IgG1k monoclonal antibody that binds to and inhibits active plasma kallikrein proteolytic activity, but without binding pre-kallikrein, the circulating inactive precursor. Lanadelumab was approved in 2018 for “prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years and older.”

The Applicant submitted the current efficacy supplement to provide data to support extension of the indication to patients 2 years of age or older, including introduction of a new 150 mg prefilled syringe presentation. Since the pathogenesis of HAE is identical between children 2 to <12 years of age and adolescents and adults ≥12 years of age, with activated kallikrein playing a key role in the affected pathway, full extrapolation of efficacy from the adequate and well-controlled trials that supported the original approval, with PK matching, is acceptable. This supplement is supported by data from a single 52-week, open-label, phase 3, PK, PD, and safety trial in pediatric patients with type I or II HAE aged 2 year to < 12 years (SPRING Trial). The study enrolled 17 subjects aged 6 to < 12 years and 4 subjects aged 2 to < 6 years. Pharmacokinetic (PK) analyses using the proposed doses demonstrate similar drug exposure levels for 150 mg administered subcutaneously every 4 weeks for patients 2 to 6 years of age or 150 mg administered subcutaneously every 2 weeks for 6 to <12 years old. The pharmacodynamic (PD) response, assessed by measurements of plasma cHMWK as a measure of plasma kallikrein enzymatic activity, was also comparable. No new safety signals were identified in the SPRING trial. Although the SPRING trial was not designed to assess efficacy given the small sample size and uncontrolled design, exploratory efficacy analysis demonstrated results consistent with the adolescent and adult trials (reduction in rate of acute exacerbations from baseline). Overall, there is a favorable benefit risk assessment for lanadelumab in the prophylaxis to prevent HAE exacerbations in patients ≥2 years of age and I agree with the review teams assessment for

approval of this efficacy supplement. Expanding the availability of lanadelumab to children 2 to < 12 years of age addresses an important unmet need for this rare disease.

15. Appendices

15.1. References

1. Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med. 2020 Mar 19;382(12):1136-1148.
2. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C'1 esterase. Am J Med.1963; 35:37-44.
3. Pancholy N, Craig T. Hereditary angioedema in children: a review and update. Curr Opin Pediatr. 2019 Dec;31(6):863-868.
4. Fay A, Abinun M. Current management of hereditary angioedema (C'1 esterase inhibitor deficiency). J Clin Pathol 2002; 55:266–270.
5. Bork K, et al.. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med 200; 119: 267–274.
6. MacGinnitie AJ. Pediatric hereditary angioedema. Pediatr Allergy Immunol. 2014 Aug;25(5):420-7.
7. Caballero, T, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. Allergy Asthma Proc. 2014; 35(1), 47-53.]

15.2. Financial Disclosure

The financial disclosure checklist for the clinical trial submitted to this sBLA is provided below. Although there were several significant payments of other sorts, these were unlikely to significantly impact the conduct of the clinical trial, given that each investigator site enrolled a small number of patients and does not impact the interpretation of the PK/PD and safety results.

Table 17. Covered Clinical Study (Name and/or Number): SPRING; DX-2930-04

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 17 principal investigators (PI) and 99 Sub-investigators (SI)		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6 PI and 1 SI		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Office of Clinical Pharmacology Appendices (Technical Documents Supporting Recommendations)

15.3.1. SPRING Trial

To support the use of lanadelumab in pediatric patients aged 2 to < 12 years, the Applicant conducted the SPRING trial, a phase 3, open-label, multicenter, PK, PD, and safety study in pediatric patients with type I or type II HAE. The primary objectives of the study were to evaluate the safety and PK of lanadelumab in children 2 to < 12 years of age with HAE. Secondary objectives included assessments of PD, based on plasma kallikrein activity, and immunogenicity. Evaluation of clinical outcomes was also a secondary objective based on the number of investigator-confirmed HAE attacks during the treatment period.

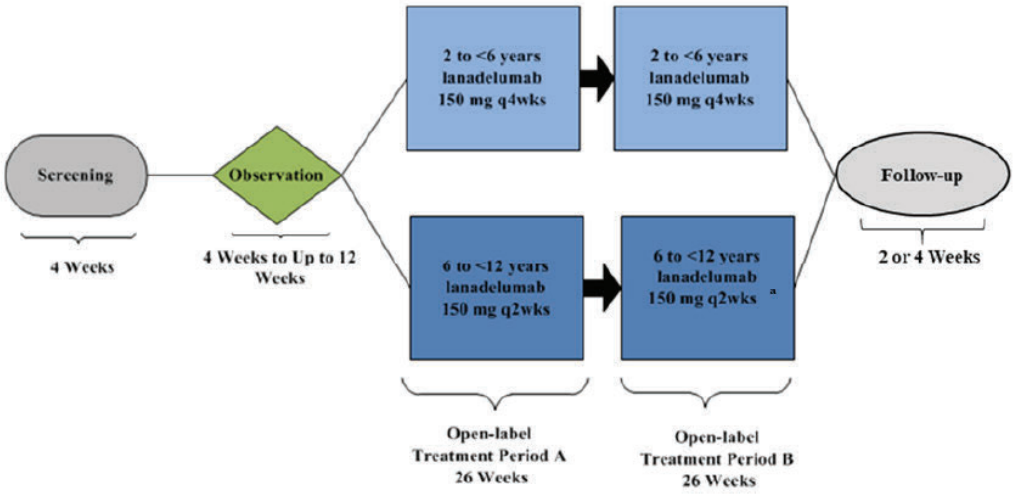
Study Design

This phase 3 trial was conducted in an open-label fashion. The study enrolled 21 pediatric subjects 2 to < 12 years of age with type I or II HAE who experienced at least one angioedema attack per three months. Subjects entered a 52-week treatment period that was comprised of two 26-week treatment periods (A and B). The dosing regimen received was based on the subject's age at enrollment (i.e., 6 to < 12 years or 2 to < 6 years). All doses were administered SC in the abdomen, thigh, or upper arm.

- Treatment Period A: Subjects aged 6 to < 12 years received 150 mg Q2W; subjects aged 2 to < 6 years received 150 mg Q4W
- Treatment Period B: Subjects aged 6 to < 12 years could remain on the same regimen, or switch to a 150 mg Q4W regimen if well-controlled (i.e., attack free) for 26 weeks; subjects aged 2 to < 6 years continued to receive 150 mg Q4W.

The study schema is shown below:

Figure 15. Study Schema



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.

Source: Figure 1, Clinical Study Report for the SPRING trial

Noteworthy Inclusion and Exclusion Criteria

Inclusion Criteria:

- Be a child (male or female) 2 to < 12 years of age at the time of screening
- Documented diagnosis of HAE (type I or II)
- Historical baseline HAE attack rate of at least 1 attack per 3 months

Exclusion Criteria:

- Had concomitant diagnosis of another form of chronic, recurrent angioedema
- Had initiated androgen treatment within 2 weeks prior to entering the observation period
- Exposed to angiotensin-converting enzyme inhibitors or any estrogen-containing medications with systemic absorption within 4 weeks prior to screening
- Had any active infectious illness of fever within 24 hours prior to the first dose of lanadelumab in Treatment Period A
- Had any HAE attack that was not resolved prior to the first dose of lanadelumab in Treatment Period A
- Had any of the following liver function test abnormalities: ALT or AST > 3x ULN, or total bilirubin > 2x ULN.

Subject Disposition and Demographics

A total of 24 subjects were screened and 21 subjects were enrolled and received at least 1 dose of lanadelumab. Overall, 20 subjects (95.2%) completed Treatment Period A, and Treatment Period B, thereby completing the study. One subject in the 2 to < 6 years age group discontinued the study within the first 3 months due to withdrawal by parent/guardian.

After completion of Treatment Period A, 7 subjects in the 6 to < 12 years age group (41.2%) qualified to switch from the Q2W to the Q4W dosing regimen due to remaining stably attack-free for 26 weeks. One subject in the 2 to < 6 years age group ((b) (6)) was switched from the Q4W to the Q2W regimen due to recurrent attacks.

The study enrolled 17 subjects aged 6 to < 12 years who received the 150 mg Q2W regimen, and 4 subjects aged 2 to < 6 years who received the 150 mg Q4W regimen. The median [range] age was 8.7 [3.5, 10.9] years. Subjects were predominantly female (n = 12, 57.1%), White (n = 20, 95.2%), and not of Hispanic or Latino ethnicity (n = 19, 90.5%). The majority of subjects had a diagnosis of type I HAE (n = 20, 95.2%) and were not on long-term prophylactic therapy for HAE (n = 18, 85.7%). Of the 3 subjects on long-term HAE prophylactic therapy, all were taking C1-INH.

In the 2 to < 6 years age group, the median [range] body weight and median [range] BMI were 21.1 [15.8, 23.5] kg and 16.2 [15.3, 18.2] kg/m^2, respectively. In the 6 to < 12 years age group, the median [range] body weight and median [range] BMI were 31.1 [19.6, 63.3] kg and 17.8 [14.1, 30.5] kg/m^2, respectively.

PK, PD and ADA Sample Collection

Plasma PK samples were collected pre-dose on Days 0, 4, 14, 28, 56, 84, 112, 140, 168, 182, 196, 252, 308, 364 (Week 52), and 392 (end of study).

Plasma PD samples for measurement of cHMWK (secondary objectives) were collected pre-dose on Days 0, 4, 14, 28, 56, 84, 112, 140, 168, 182, 196, 252, 308, 364, and 392.

Plasma PD samples for measurement of C1-INH and C4 (exploratory objectives) were collected pre-dose on Days 0, 28, 56, 84, 112, 140, 168, 182, 196, 252, 308, 364, and 392.

Plasma ADA samples were collected pre-dose on Days 0, 28, 84, 140, 182, 196, 252, 308, 364, and 392.

Samples on Days 4, 14 (Q4W dosing only), 182, and at the end of study visit could be collected at any time of day.

PK, PD, and ADA Analysis

The PK analysis set included all subjects who received any study drug with at least 1 evaluable post-dose PK concentration value. Similarly, the PD analysis set draws from the same population, but includes those who have at least 1 evaluable post-dose PD value.

Descriptive summary analyses of lanadelumab plasma concentrations, cHMWK levels, C1-INH, and C4 by nominal time point were performed. PK and PD properties were also evaluated using a population modeling and simulation approach that incorporated data from the present study (SPRING trial) as well as other clinical studies in the lanadelumab development program conducted in adult and adolescent subjects aged 12 years and older. For additional details on the population PK methodology and analysis, refer to the Pharmacometrics Review in Section 15.3.3.

Immunogenicity was evaluated based on the number and percentage of subjects with positive ADAs and whether they were neutralizing or non-neutralizing. Data was summarized by study visit and overall. The effect of immunogenicity on PK, PD, clinical outcomes, and safety was also assessed.

Exclusions

All 21 subjects were included in the safety, PK, and PD analysis sets. This includes the one subject who discontinued the study prematurely.

Note that for one subject ((b) (6)) in the 6 to < 12 years age group, PK, PD, and immunogenicity information is only available through Day 14. On-site study visits for this subject were conducted remotely starting at Day 28 through the end of the study due to the COVID-19 pandemic. This subject was overall considered as having completed the study and is included in the PK, PD, and immunogenicity analysis sets.

15.3.2. Bioanalytical Methods

PK Bioanalytical Method (A11347B1-SHP643)

For the SPRING trial, lanadelumab concentrations were quantified in human plasma samples using Method QC-52-25 – Quantitation of DX-2930 (lanadelumab) in Human SCAT 169 Plasma Samples by ELISA. A validation report for this method of evaluating lanadelumab concentrations (A8527-SHP643) was previously submitted under BLA 761090 SDN 5, submitted Dec. 26, 2017. The method used to quantitate lanadelumab in samples from the SPRING trial is the same as that used on samples from previously submitted studies supporting approval of the original BLA.

The method uses an anti-DX-2930 Fab antibody as the capture reagent. Bound lanadelumab is then bound to a biotinylated anti-DX-2930 antibody, which is then detected with streptavidin-conjugated horseradish peroxidase. Addition of 3,3’,5,5’-tetramethylbenzidine (TMB) is added to develop the signal, followed by quenching with an acidic stop solution. Determination of absorption at 450 nm is used to measure the amount of lanadelumab in samples. The LLOQ of the assay is 3.13 ng/mL.

Table 18. Method Performance in SPRING Trial

Assay Passing Rate	28/28 runs met the method acceptance criteria	Yes
Standard curve performance	Except for masked samples, all standard curve samples across all runs fell within ± 15% of the nominal value (± 20% for the LLOQ)	Yes
QC performance	Across all runs, QC performance met acceptance criteria based on at least 4/6 samples falling within ± 20% of the nominal values, and at least one QC sample at each level (high, medium, and low) falling within ± 20% of the nominal value.	Yes
Method reproducibility	Incurred sample reanalysis was performed for 27/264 samples (10.2%). 26/27 samples (96.3% met acceptance criteria based on percent difference ≤ 30% of the mean.	Yes
Study sample analysis/ stability	All samples were stored at -80 °C until analysis. All samples were analyzed between Mar. 25, 2020, and Nov. 10, 2021. All samples were analyzed within the established stability of 20 months at -80 °C.	

Source:
Abbreviations: LLOQ, lower limit of quantification; QC, quality control

Note that the bioanalytical method protocol specifies that up to 2/8 standards not meeting criteria for accuracy and precision may be masked to improve curve fit. If the LLOQ of the curve is masked, the LLOQ for that plate is the lowest point of the curve to meet the acceptability criteria. For 5/28 runs, the LLOQ sample (concentration of 3.125 ng/mL) was masked. Thus, for these runs, the LLOQ was the next lowest standard (concentration of 6.250 ng/mL). Most samples marked as below the limit of quantitation (BLQ) were samples collected prior to dose administration (Day 0), where measurement of lanadelumab concentrations would not be expected. One sample collected on Day 4 and another sample collected on Day 168 (in two separate subjects) were also marked as BLQ.

Overall, the bioanalytical performance for quantitation of lanadelumab in human plasma samples in the SPRING trial is acceptable.

PD Bioanalytical Method (A11347B-SHP643)

In the SPRING trial, cleaved high molecular weight kininogen (HMWK), an endogenous substrate of plasma kallikrein, was measured as a PD biomarker in human sodium citrate plasma samples using Method SOP RD-DYA-002 – HMWK Biomarker Assay without Factor XIIa Activation by Western. Two qualification reports for this method of evaluating the percent HMWK in plasma via Western blot (A8197M-SHP643 and A8022M-SHP643) were previously submitted under BLA 761090 SDN 5, submitted Dec. 26, 2017. The method used to quantitate the percent cleaved HMWK in samples from the SPRING trial is the same as that used on samples from previously submitted studies supporting approval of the original BLA.

The Western blotting method involves detection of HMWK using a mouse monoclonal anti-LC HMWK antibody, which is subsequently detected using a goat anti-mouse IRDye 680. The excitation signal of the IRDye 680 is used for quantification. Using this method, three species are visible: 1) intact HMWK (110 kDa); 2) cleaved HMWK, two heavy chains (56 kDa); and 3) cleaved HMWK, two light chains (46 kDa). The percent of cleaved HMWK is calculated as the

ratio of combined signals of bands at 56 and 46 kDa to the total signal from all bands at 110, 56, and 46 kDa.

A total of 267 unique samples (from 270 total samples) were analyzed. Acceptance criteria for test bands was based on the integrity of the membrane and identification of bands at 110, 56, and 46 kDa.

15.3.3. Pharmacometrics Review

15.3.3.1. Population PK Analysis

15.3.3.1.1. Review Summary

In general, the Applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of lanadelumab for long-term prophylaxis against acute attacks of hereditary angioedema (HAE) in pediatric patients 2 to < 12 years of age. Previously, lanadelumab has been approved in adult and adolescent patients (12 years and older) [1]. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. More specifically, the model was used to support the current submission as outlined in summary Table 24.

[1] DARRTS, Action date: 8/23/2018

Table 19. Specific Comments on Applicant's Final Population PK model

Utility of the Final Model		Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors		
Intrinsic factor	Population pharmacokinetic analyses showed that age, gender, and race did not meaningfully influence the pharmacokinetics of lanadelumab-flyo after correcting for body weight. Body weight was identified as an important covariate describing the variability of clearance and volume of distribution, resulting in higher exposure (AUC and Cmax) in lighter patients. However, this difference is not considered to be clinically relevant and no dose adjustments are recommended for any of these demographics. Based on population pharmacokinetic analysis, renal impairment (estimated GFR: 60 to 89 mL/min/1.73m^2, [mild, N=98] and 30 to 59 mL/min/1.73m^2, [moderate, N=9]) had no effect on the clearance or volume of distribution of lanadelumab-flyo.	The statement is acceptable. Please refer to **Section 15.3.3.1.4** for details.
Extrinsic factor	N/A	N/A
Support Applicant's proposed labeling statements about pediatric population		
	Based on population pharmacokinetics (PK) analyses, the mean lanadelumab-flyo C_{ave} was approximately 2 (b)(4)% higher following SC administration of TAKHZYRO 300 m (b)(4) q2wks in pediatric patients 12 to less than 18 years of age than the mean C_{ave} in adult patients under the same dosing regimen, due to lower body weight in pediatric patients. The mean lanadelumab-flyo C_{ave} was approximately (b)(4)% higher following SC administration of TAKHZYRO 150 mg q2wks in pediatric patients 6 to less than 12 years of age than the mean Cave in adult patients receiving 300 mg q2wks. The mean lanadelumab-flyo C_{ave} was approximately 14% lower following SC administration of TAKHZYRO 150 mg q4wks in pediatric patients 2 to less than 6 years of age.	The statement is acceptable. These values are calculated based on simulation in 1000 virtual patient population as described in **Section 15.3.3.1.4** (**Figure 25**).

Source:
Abbreviations: AUC: area under the concentration time curve; C_{ave}: average plasma concentration; GFR: glomerular filtration rate; N/A: not applicable; PK: pharmacokinetics; SC: subcutaneous

15.3.3.1.2. Introduction

The primary objectives of Applicant's analysis were to perform pharmacokinetic (PK), pharmacodynamic (PD) and exposure-response (ER) analyses to support dosing of lanadelumab in pediatric subjects 2 to <12 years of age.

15.3.3.1.3. Model Development

Data

The pooling of data collected in pediatric subjects 2 to < 12 years of age (SPRING trial) as well as adolescent and adult subjects (Study #DX-2930-01, DX-2930-02, DX-2930-03 and DX-2930-04) was performed to support dosing of lanadelumab in pediatric subjects 2 to <12 years of age. The PopPK analysis was performed based on data collected in 278 subjects and 3476 post-dose samples collected across studies (not including placebo groups). A total of 21 (7.6%) pediatric patients with HAE (2 to < 12 years) had at least one PK and PD sample in the SPRING trial 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. BLQ values (2.3% of the total sample) were set to missing. Brief descriptions of the studies included are presented in Table 20.

Phoenix NLME (Version 8.3) was used for PopPK modeling. Dataset construction, exploration and figures were performed using R (Version 4.1 or higher).

Table 21 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 20. Summary of Studies With PK Sampling Included in Population PK Analysis

Study # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type and Food Status	Dose(s)
DX-2930-01 Phase 1	Subjects were randomized to receive placebo or active study drug within one of the following sequential, ascending dose cohorts: 0.1, 0.3, 1.0, or 3.0 mg/kg. A Phase 1, Double-Blind, Single Ascending Dose Study to Assess Safety, Tolerability and PK of DX-2930 in Healthy Subjects	N=24 Healthy adults	0.1, 0.3, 1.0, or 3.0 mg/kg
DX-2930-02 Phase 1b	Subjects were to receive 30, 100, 300 or 400 mg. A Phase 1b, Double-Blind, Multiple Ascending Dose Study to Assess Safety, Tolerability and Pharmacokinetics of DX- 2930 in HAE Subjects	N=24 Adult HAE patients	30, 100, 300 or 400 mg.
DX-2930-03	Subjects were randomized 2:1 to receive DX-2930 or placebo in a double - blind fashion. Subjects who were randomized to DX-2930 were assigned in a 1:1:1 ratio to one of three dose regimens: 300 mg every 2 weeks, 300 mg every 4 weeks or 150 mg every 4 weeks. A Multicenter, Randomized, Double- Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of HAE "HELP™ Study"	N=84 Adult and adolescent HAE patients	300 mg Q2W, 300 mg Q4W, and 150 mg Q4W

Study # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type and Food Status	Dose(s)
DX-2930-04 HELP Study Extension	Rollover Subjects Rollover subjects received a single open-label dose of 300 mg SHP643 administered subcutaneously (SC) on Day 0. After the first recorded HAE attack, then received repeated SC administrations of open label 300 mg SHP643 every 2 weeks for up to 350 days. Non-rollover Subjects Subjects received repeated SC administrations of open label 300 mg SHP643 every 2 weeks for up to 350 days An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of HAE	N=109 (rollover subjects) N=103 (non-rollover subjects) Adult and adolescent HAE patients	300 mg Q2W
SPRING Trial An Open-Label, Multicenter, Phase 3 Study	Treatment Period A: Subjects first entered Treatment Period A, whereby subjects 2 to <6 years received lanadelumab 150 mg Q4W, and subjects 6 to <12 years received lanadelumab 150 mg Q2W. After completion of the first 26-week treatment period, subjects were to immediately continue into Treatment Period B. Treatment Period B: Subjects in Treatment Period B received lanadelumab for an additional 26 weeks (total of 52 weeks). During these additional 26 weeks, subjects 2 to <6 years continued receiving 150 mg Q4W. For subjects 6 to <12 years, they may either remain on the same dose regimen as Treatment Period A or may switch to lanadelumab 150 mg Q4W if they have been well-controlled (e.g., attack free) for 26 consecutive weeks with lanadelumab treatment. Evaluate the Safety, PK, and of Lanadelumab for Prevention Against Acute Attacks of HAE in Pediatric Subjects 2 to <12 Years of Age	N=21 2 to <12 years HAE patients	150 mg Q4W (2 to <6) 150 mg Q2W or 150 mg Q4W (6 to <12

Source: Table adapted from Table 1, 2 and 4, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Note: DX-2930 is the former name of lanadelumab SHP643)
Abbreviations: HAE: heredity angioedema; PK: pharmacokinetics: PopPK: population pharmacokinetics; Q2W: every 2 weeks: Q4W: every 4 weeks;

Table 21. Summary of Baseline Demographic Covariates for Analysis (Categorical Covariates)

Baseline Characteristics		N(%)					
		Other Studies (Adults and Adolescents)					Pediatric Study (2 to <12 years)
		DX-2930-01 (N=24)	DX-2930-02 (N=24)	DX-2930-03 (N=84)	DX-2930-04 (N=109) Rollover Subjects*	DX-2930-04 (N=103) Non-Rollover Subjects**	SHP643-301 (N=21)
Age	Child (2 to <6 years)	-	-	-	-	-	4 (19.0%)
	Child (6 to <12 years)	-	-	-	-	-	17 (81.0%)
	Adolescent (12 to <18 years)	-	-	6 (7.1%)	8 (7.3%)	13 (12.6%)	-
	Adult (≥18 years)	24 (100%)	24 (100%)	78 (92.9%)	101 (92.7%)	90 (87.4%)	-
Sex	Female	11 (45.8%)	16 (66.7%)	54 (64.3%)	75 (68.8%)	68 (66.0%)	12 (57.1%)
	Male	13 (54.2%)	8 (33.3%)	30 (35.7%)	34 (31.2%)	35 (34.0%)	9 (42.9%)
Race	Asian	-	-	2 (2.4%)	2 (1.8%)	-	1 (4.8%)
	Black or African American	14 (58.3%)	-	8 (9.5%)	8 (7.3%)	2 (1.9%)	-
	Multiple	-	-	-	-	1 (1.0%)	-
	Other and AIAA	-	-	-	-	1 (1.0%)	-
	White	10 (41.7%)	24 (100%)	74 (88.1%)	99 (90.8%)	99 (96.1%)	20 (95.2%)
HAE Attack Status and Severity at Baseline[a]	None	24 (100%)	12 (50.0%)	-	-	19 (18.4%)	0 (0%)
	Mild	-	6 (25.0%)	17 (20.2%)	19 (17.4%)	11 (10.7%)	4 (19.0%)
	Moderate	-	4 (16.7%)	50 (59.5%)	66 (60.6%)	39 (37.9%)	14 (66.7%)
	Severe	-	2 (8.3%)	17 (20.2%)	24 (22.0%)	34 (33.0%)	3 (14.3%)
Duration of HAE Attack at Baseline[a]	No Attacks	24 (100%)	16 (66.7%)	-	-	16 (15.5%)	0 (0%)
	<12 Hours	-	2 (8.3%)	17 (20.2%)	23 (21.1%)	2 (1.9%)	8 (38.1%)
	>48 Hours	-	2 (8.3%)	20 (23.8%)	27 (24.8%)	1 (1.0%)	5 (23.8%)
	12-24 Hours	-	4 (16.7%)	21 (25.0%)	29 (26.6%)	-	1 (4.8%)
	24-48 Hours	-	-	26 (31.0%)	30 (27.5%)	-	7 (33.3%)
	Missing		-	-	-	84 (81.6%)	-
Renal Impairment[b]	Normal Renal Function	16 (66.7%)	8 (33.3%)	33 (39.3%)	50 (45.9%)	54 (52.4%)	20 (95.2%)
	Mild Renal Impairment	8 (33.3%)	13 (54.2%)	49 (58.3%)	57 (52.3%)	42 (40.8%)	1 (4.8%)
	Moderate Renal Impairment	-	3 (12.5%)	2 (2.4%)	2 (1.8%)	7 (6.8%)	-

AIAA = American Indian or Alaska Native; eGFR = estimated glomerular filtration rate; HAE = hereditary angioedema
[a] Baseline is representative of historical HAE attack up to 3 month prior to enrollment in study DX-2930-02 and HAE attack observed over the run-in period (4 weeks) in study DX-2930-03 and DX-2930-04 (non-rollover). For rollover subjects in DX-2930-04, the baseline from DX-2930-03 was used.
[b] Normal renal function (eGFR ≥ 90 mL/min/1.73m^2), mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73m^2), and moderate renal impairment (eGFR ≥ 30 to < 60 mL/min/1.73m^2). eGFR was estimated using the MDRD equation for adults and the Bedside Schwartz equation for patients less than <18 years of age
* A total of 76 subjects in study DX-2930-03 who received lanadelumab treatments enrolled in study DX 2930-04 as rollover subjects. In addition, 33 subjects in study DX-2930-03 who received placebo enrolled in study DX 2930-04 as rollover subjects.
** A total of 19 subjects enrolled in study DX-2930-02 subsequently enrolled in study DX-2930-04 as non-rollover subjects

Baseline Characteristics	Mean (CV%) Median [Min, Max]					
	Other Studies (Adults and Adolescents)					Pediatric Study (2 to <12 years)
	DX-2930-01 (N=24)	DX-2930-02 (N=24)	DX-2930-03 (N=84)	DX-2930-04 (N=109) Rollover Subjects*	DX-2930-04 (N=103) Non-Rollover Subjects**	SHP643-301 (N=21)
Age (years)	32.5 (30.4%) 29.0 [20.0, 52.0]	39.3 (35.9%) 36.5 [20.0, 68.0]	40.6 (33.6%) 42.0 [12.0, 73.0]	41.4 (35.6%) 43.0 [12.0, 73.0]	39.0 (43%) 39.0 [12.0, 75.0]	7.52 (26.8%) 8.00 [3.00, 10.0]
Weight (kg)	79.7 (17.5%) 78.3 [54.5, 111]	83.1 (30.7%) 76.0 [55.0, 161]	82.1 (24.5%) 78.5 [46.8, 150]	80.1 (27.1%) 75.5 [36.7, 150]	80.8 (31.2%) 76.0 [44.2, 178]	32.0 (39.5%) 29.9 [15.8, 63.3]
Height (cm)	174 (6.44%) 174 [155, 202]	171 (4.83%) 170 [157, 187]	169 (5.24%) 168 [152, 195]	168 (5.54%) 167 [145, 195]	168 (5.67%) 168 [149, 195]	130 (11.3%) 132 [102, 158]
BMI (kg/m^2)	26.2 (12.9%) 27.1 [18.4, 32.1]	28.4 (28.4%) 26.0 [18.1, 57.0]	28.7 (21.5%) 27.2 [18.3, 47.6]	28.3 (24.2%) 27.1 [16.9, 55.0]	28.2 (26.2%) 26.1 [17.5, 50.3]	18.4 (22.4%) 17.6 [14.1, 30.5]
ALT (U/L)	23.1 (57.3%) 19.0 [10.0, 57.0]	23.1 (50.0%) 19.0 [9.00, 54.0]	25.3 (67.5%) 18.5 [9.00, 80.0]	23.3 (64.8%) 18.0 [9.0, 80.0]	23.3 (84.5%) 18 [5, 171]	14.6 (32.5%) 14.0 [7.00, 27.0]
AST (U/L)	23.0 (21.6%) 21.5 [16.0, 34.0]	19.8 (37.6%) 18.0 [9.00, 38.0]	22.3 (45.8%) 20.5 [10.0, 80.0]	21.8 (41.6%) 20.0 [11.0, 80.0]	20.8 (49.1%) 19.0 [6.00, 89.0]	26.0 (21.1%) 25.0 [15.0, 37.0]
Total Bilirubin (mg/L)	10.5 (37.9%) 10.3 [5.13, 22.2]	7.21 (58.8%) 6.84 [3.00, 17.1]	7.44 (71.1%) 5.13 [0.855, 25.7]	7.08 (68.8%) 5.13 [0.855, 25.7]	6.84 (61.2%) 6.00 [2.00, 27.0]	4.02 (46.0%) 2.91 [2.57, 8.89]
CRCL (mL/min)	128 (19.7%) 126 [81.3, 177]	120 (29.3%) 120 [49.2, 174]	125 (31.2%) 119 [53.7, 266]	123 (31.4%) 118 [53.1, 263]	131 (42.1%) 118 [35.5, 334]	168 (30.8%) 168 [75.1, 287]
eGFR (mL/min/1.73m^2)	104 (23.5%) 98.5 [69.0, 153]	83.9 (27.3%) 79.5 [41.0, 149]	88.8 (21.4%) 86.0 [36.0, 154]	89.6 (21.5%) 87.0 [36.4, 154]	90.6 (25.1%) 89.7 [30.1, 159]	176 (29.5%) 167 [98.3, 273]
Scr (mg/dL)	78.5 (24.5%) 79.6 [53.0, 106]	78.5 (21.9%) 73.8 [42.0, 131]	74.2 (23.9%) 71.6 [43.3, 133]	72.0 (23.6%) 69.9 [38.0, 133]	71.9 (25.5%) 71.0 [39.0, 158]	29.5 (35.9%) 26.5 [17.7, 53.0]
Mean HAE Severity at Baseline	NA	0.833 (121%) 0.500 [0.00, 3.00]	1.75 (29.8%) 2.00 [1.00, 3.00]	1.78 (28.9%) 2.00 [1.00, 3.00]	1.49 (57.9%) 1.67 [0.00, 3.00]	1.70 (23.9%) 2.00 [1.00, 2.00]
Rate of Monthly HAE Attack at Baseline*	NA	0.826 (119%) 0.219 [0.00, 3.00]	3.48 (63.8%) 3.00 [0.966, 10.5]	3.52 (70.5%) 3.00 [0.970, 14.0]	2.53 (108%) 1.83 [0.00, 15.2]	1.80 (85.5%) 1.43 [0.417, 6.67]
Baseline C1-inhibitor Functional Activity (%)	NA	20.1 (81.4%) 17.0 [0.00, 81.0]	21.2 (64.2%) 21.0 [0.00, 58.0]	21.1 (61.2%) 21.0 [0.00, 49.0]	19.0 (110%) 16.00 [0.00, 127]	21.6 (81.3%) 24.0 [0, 50.0]
Baseline C4 Concentrations (ng/mL)***	NA	66100 (58.7%) 58000 [22000, 163000]	80000 (106%) 59000 [6000, 660000]	77100 (102%) 59000 [6000, 660000]	86100 (67.9%) 79500 [6000, 312000]	55900 (53.1%) 47000 [15000, 150000]

Source: Table 3 and 4, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Baseline is representative of historical HAE attack up to 3 month prior to enrollment in study DX-2930-02 and HAE attack observed over the run-in period (4 weeks) in study DX-2930-03 and DX-2930-04.
A total of 76 subjects in study DX-2930-03 who received lanadelumab treatments enrolled in study DX 2930-04 as rollover subjects. In addition, 33 subjects in study DX-2930-03 who received placebo enrolled in study DX 2930-04 as rollover subjects.
** A total of 19 subjects enrolled in study DX-2930-02 subsequently enrolled in study DX-2930-04 as non-rollover subjects

*** n=102 for study DX-2930-04 non-rollover group only (Subject DX-2930-04-(b) (6) had missing baseline C4 value)
Abbreviations: ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; CRCL: creatinine clearance; CV: coefficient of variability; eGFR: estimated glomerular filtration rate; Min: minimum; Max: maximum; N: number of subjects; NA: not available; Scr: serum creatinine.

Base Model

Previously, a one compartment model with linear elimination and first-order rate of absorption (Ka) was used to characterize the concentration-time profiles of lanadelumab in original submission. In current supplement, allometric functions relating body weight to the CL/F and V/F were included as part of the model (estimated exponents) as body weight was previously demonstrated to be an important covariate describing the PK of mAbs. The formulation effect was removed in current model as it was not deemed clinically relevant in current application. Health status on CL/F was retained in current analysis. The above PopPK model was used to simultaneously assess the concentration-time profiles of lanadelumab in pediatric and non-pediatric subjects.

Covariate Analysis

A covariate analysis was performed to determine the impact of age on the CL/F and V/F of lanadelumab. Based on a population PK model using estimated body weight exponent on CL/F and V/F (0.873 and 0.907, respectively), as well as health status on CL/F, a statistically significant effect of age was observed on CL/F and V/F in the first step of the analysis at the $p<0.01$ level, however the effect of age was not significant during the backward elimination step ($p<0.001$ level) and was therefore, dropped from the model. When using fixed exponent (0.75 and 1 for CL/F and V/F, respectively), the effect of age on CL/F and V/F were not statistically significant effect at the $p<0.01$ level.

15.3.3.1.4. Final Model

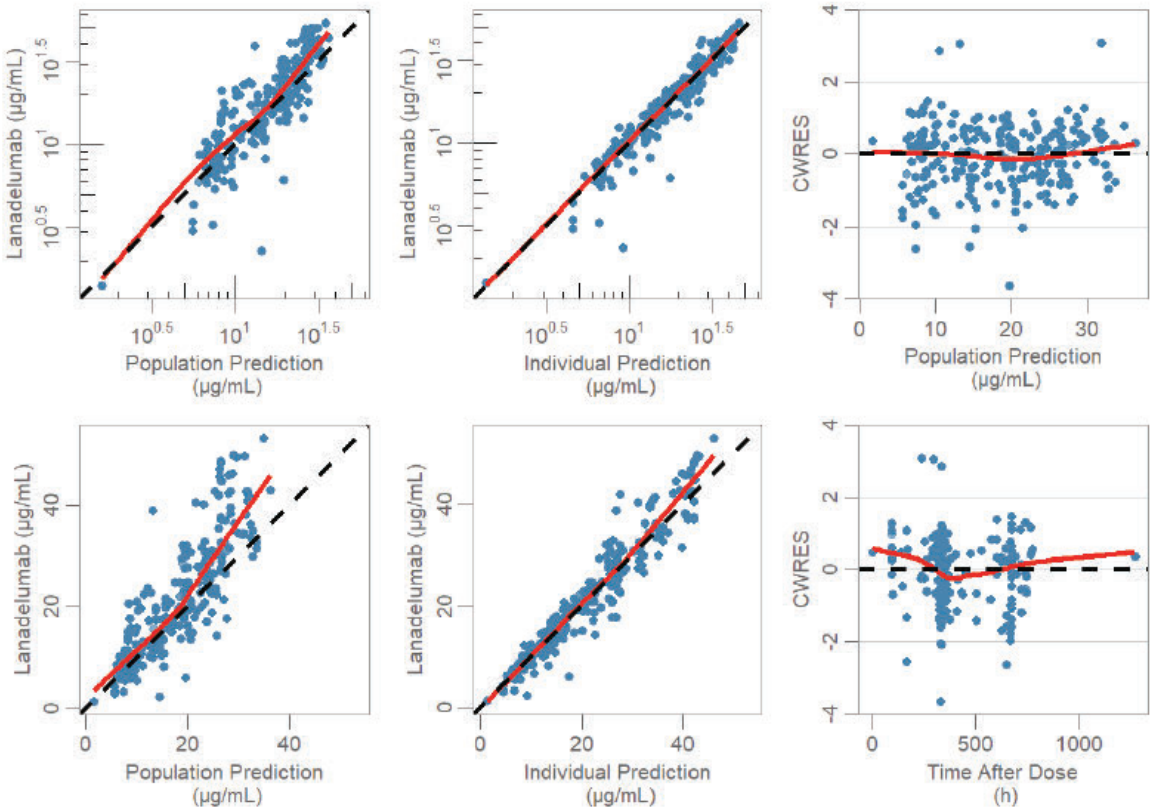
The final model included the effect of body weight of CL/F and V/F using fixed exponents (i.e. 0.75 and 1, respectively), and the effect of health status (healthy volunteers and patients with HAE) on the CL/F of lanadelumab. The final PopPK model estimates are listed in Table 22. The goodness-of-fit (GOF) plots for the SPRING trial derived with the final PopPK model are listed in Figure 16. pcVPCs (prediction-corrected visual predictive checks) plots are listed in Figure 17. Overall, the observed concentrations versus both individual predicted and population predicted values fell along the line of identity for all studies as well as the SPRING trial.

Table 22. Population Parameter Estimate for the Final PopPK Model

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)	-

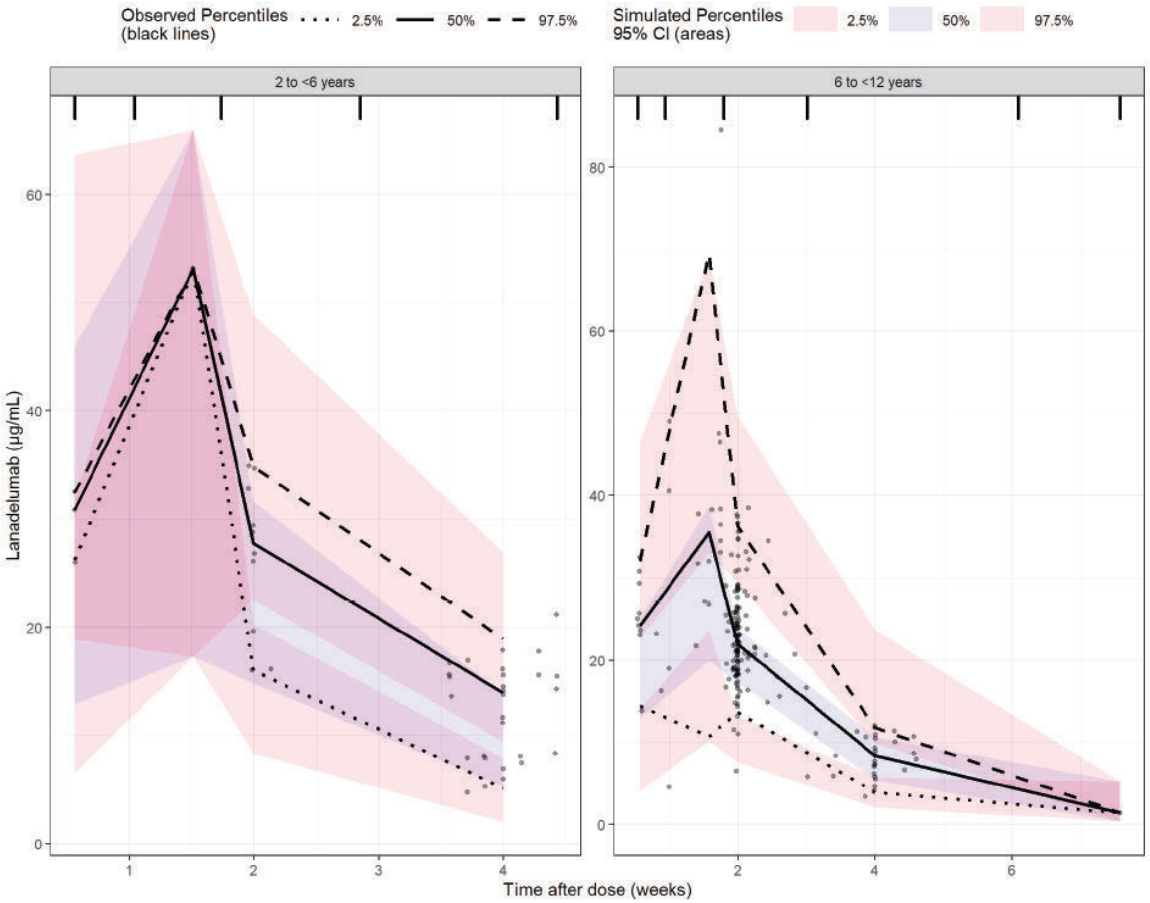
Source: Table 5, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Note 1: Population PK parameters are presented for 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.
Abbreviations: 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; NA: not applicable; RSE: relative standard error; V/F: apparent volume of distribution; WT: body weight.

Figure 16. Goodness-of-Fit Plots for Final PopPK Model of Lanadelumab – SPRING Trial



Source: Figure 7, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Black dotted line is the line of identity; red solid line is the LOESS (locally weighted smoothing scatterplot function); dots are individual values.
Abbreviations: popPK: population pharmacokintics

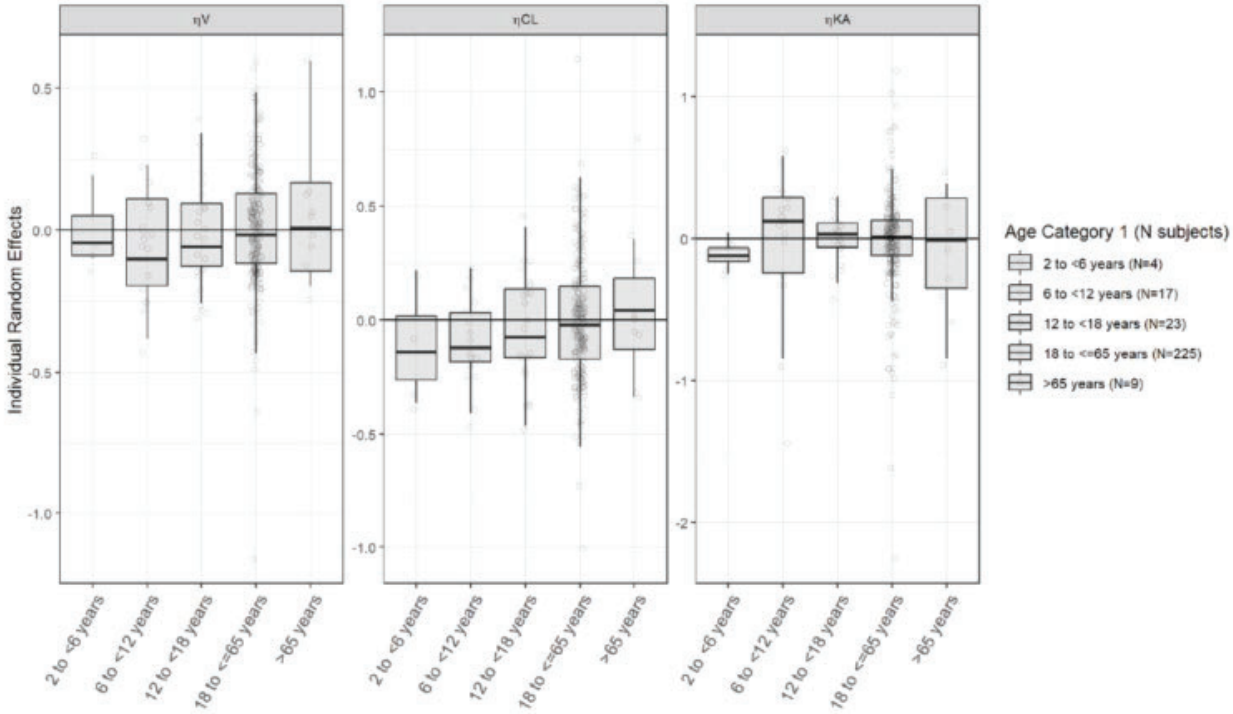
Figure 17. pcVPCs to Externally Validate the Predictive Performance of the Final PopPK Model (SPRING Trial)



Source: Section 11.35, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Note: grey circles represent observations; simulated concentrations lower than the BLQ were not considered
Abbreviations: pcVPC: prediction-corrected visual predictive check; popPK: population pharmacokinetics

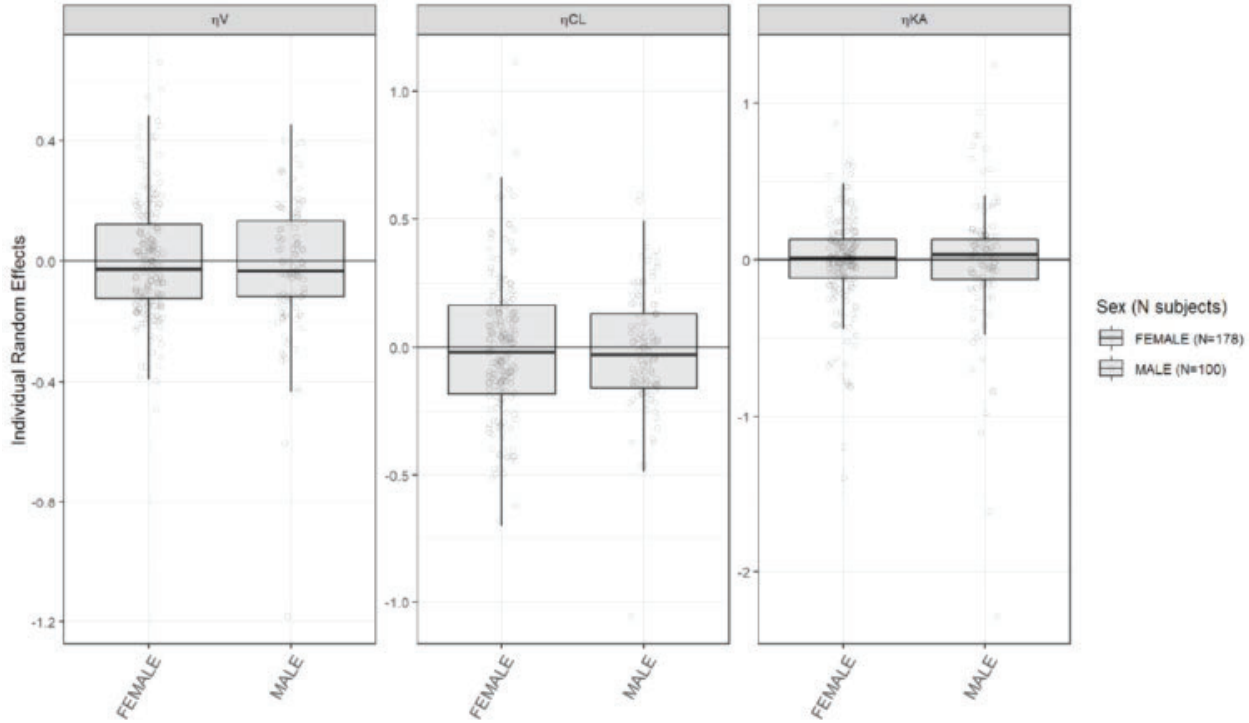
The impact of the covariates of interest on lanadelumab PK was assessed by graphical evaluation of the model parameters with random effects. Based on graphical exploration, no residual effects of sex, markers of liver/renal function (i.e., AST, ALT, total bilirubin, estimated glomerular filtration rate [eGFR]), liver/renal impairment categories, body site injection (upper arm, thigh, or abdomen) or type of administration (≥80% or <80% of the doses self-administered) were identified confirming the none of these covariates affected the PK of lanadelumab (Figure 18).

Figure 18. Correlation of Interindividual Random Effects With Covariates (Age)



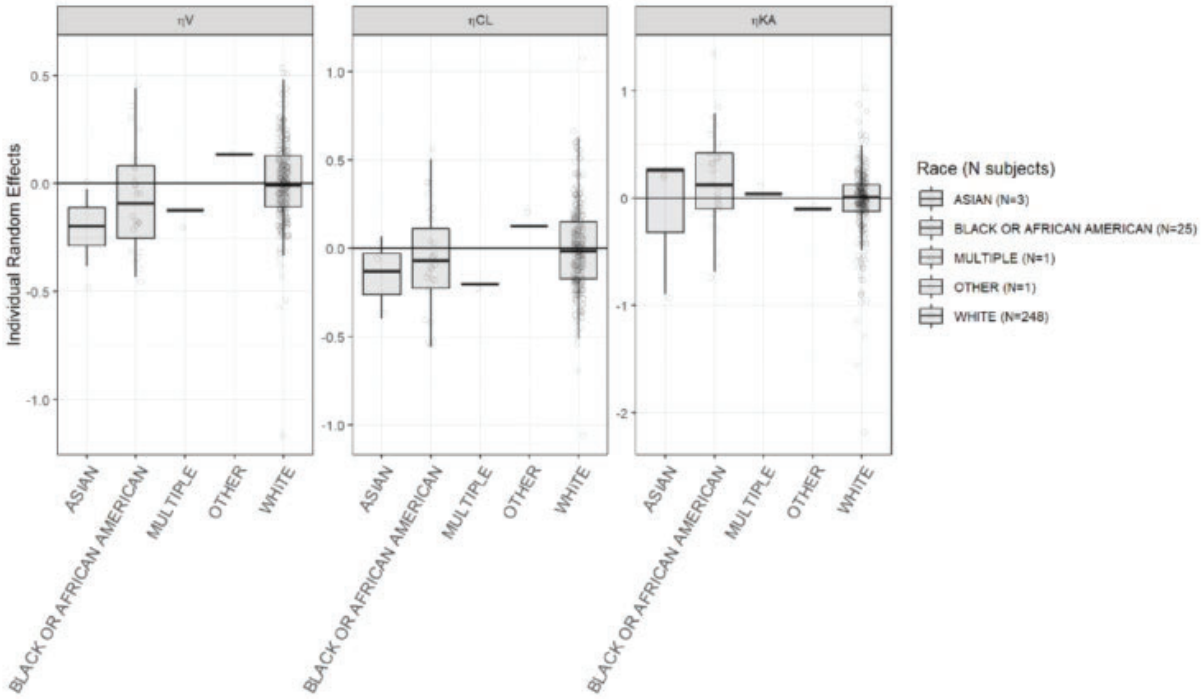
Source: Section 11.9, 11.11, 11.12, 11.13, 11.14 and 11.18 Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab SHP643 for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: ηCL: Random Effect on Clearance; ηKA: Random Effect on Absorption Rate; ηV: Random Effect on Central Volume of Distribution

Figure 19. Correlation of Interindividual Random Effects With Covariates (Gender)



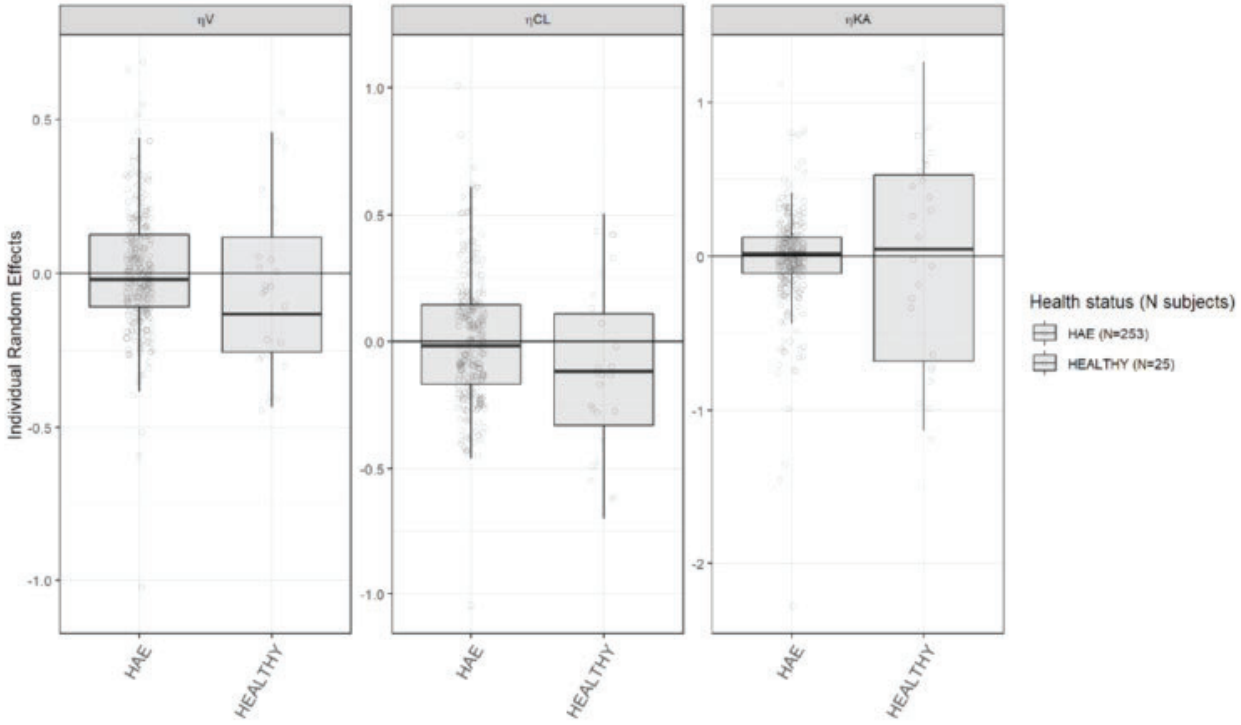
Source: Section 11.9, 11.11, 11.12, 11.13, 11.14 and 11.18 Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab SHP643 for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: ηCL: Random Effect on Clearance; ηKA: Random Effect on Absorption Rate; ηV: Random Effect on Central Volume of Distribution

Figure 20. Correlation of Interindividual Random Effects With Covariates (Race)



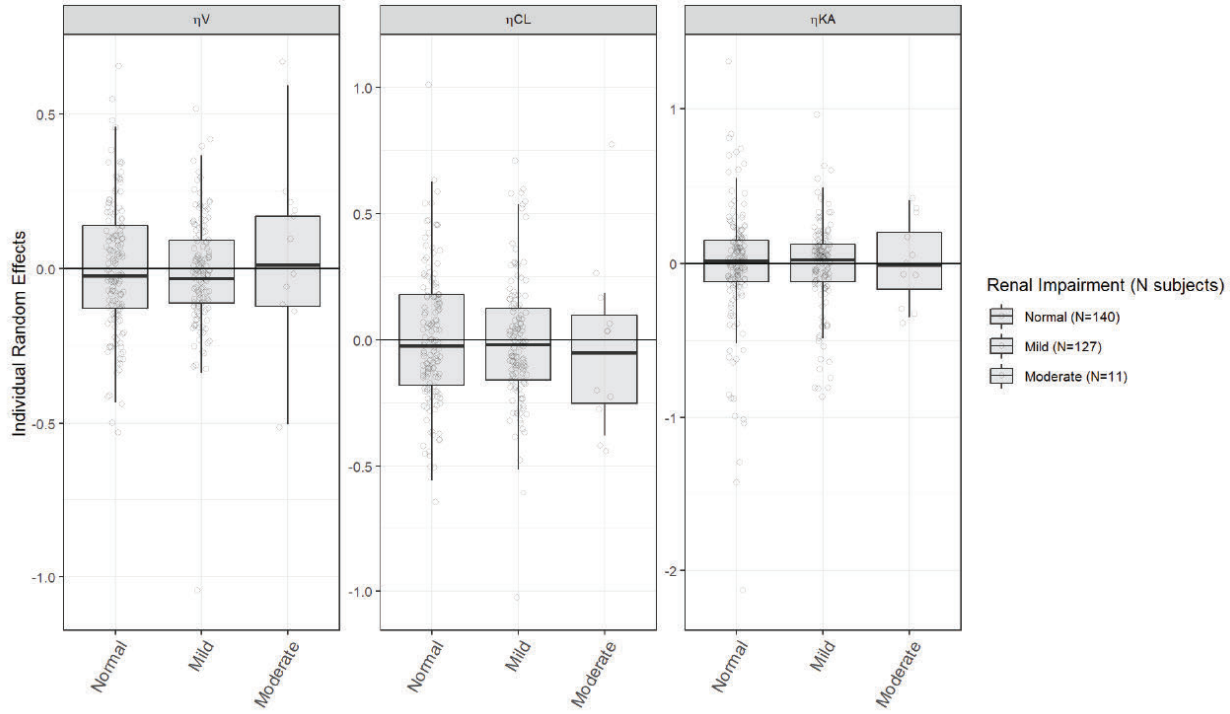
Source: Section 11.9, 11.11, 11.12, 11.13, 11.14 and 11.18 Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab SHP643 for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: ηCL: Random Effect on Clearance; ηKA: Random Effect on Absorption Rate; ηV: Random Effect on Central Volume of Distribution

Figure 21. Correlation of Interindividual Random Effects With Covariates (Health Status)



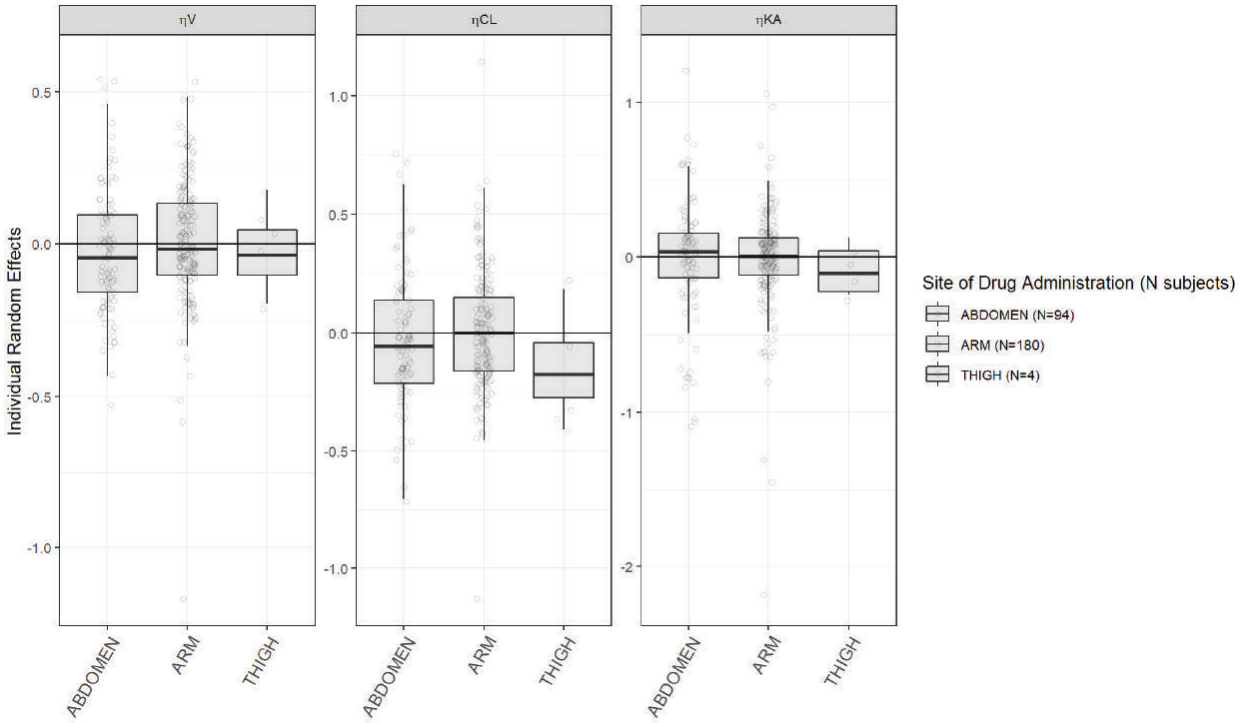
Source: Section 11.9, 11.11, 11.12, 11.13, 11.14 and 11.18 Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab SHP643 for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: ηCL: Random Effect on Clearance; ηKA: Random Effect on Absorption Rate; ηV: Random Effect on Central Volume of Distribution

Figure 22. Correlation of Interindividual Random Effects With Covariates (Renal Impairment Status)



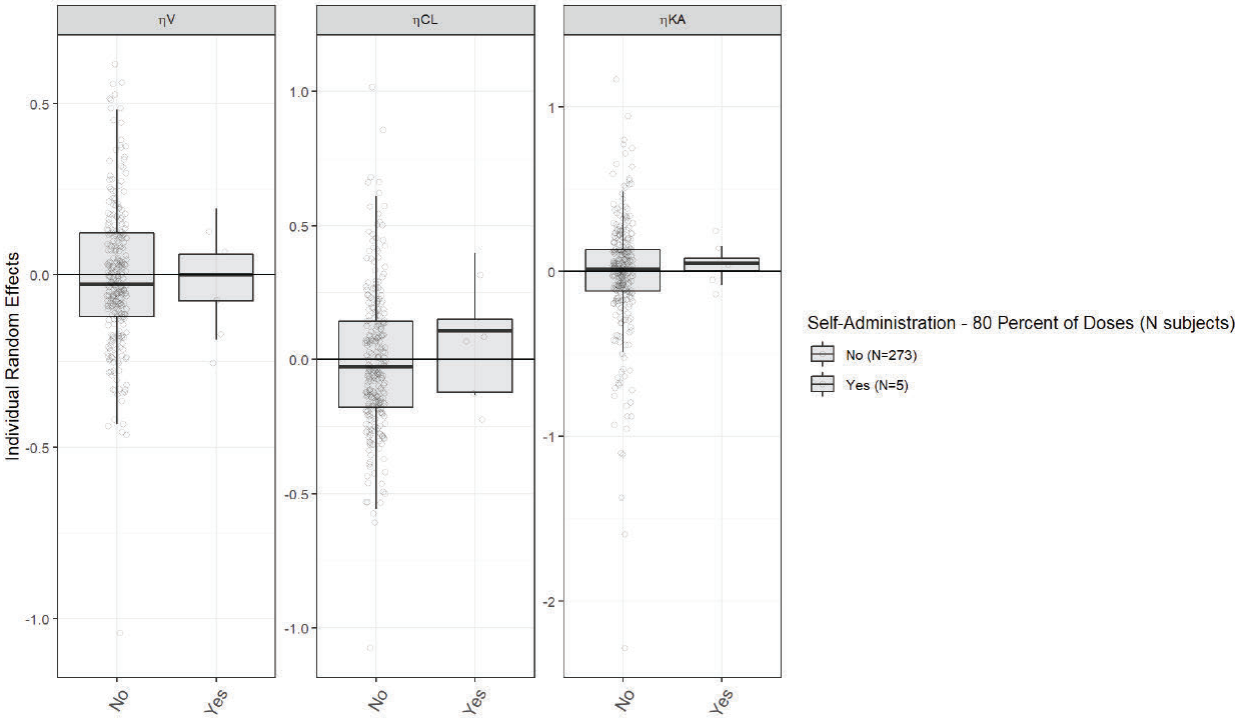
Source: Section 11.9, 11.11, 11.12, 11.13, 11.14 and 11.18 Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab SHP643 for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: ηCL: Random Effect on Clearance; ηKA: Random Effect on Absorption Rate; ηV: Random Effect on Central Volume of Distribution

Figure 23. Correlation of Interindividual Random Effects With Covariates (Site of Drug Administration)



Source: Section 11.9, 11.11, 11.12, 11.13, 11.14 and 11.18 Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab SHP643 for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: ηCL: Random Effect on Clearance; ηKA: Random Effect on Absorption Rate; ηV: Random Effect on Central Volume of Distribution

Figure 24. Correlation of Interindividual Random Effects With Covariates (Self-Administration for ≥80% of the Treatment Duration)

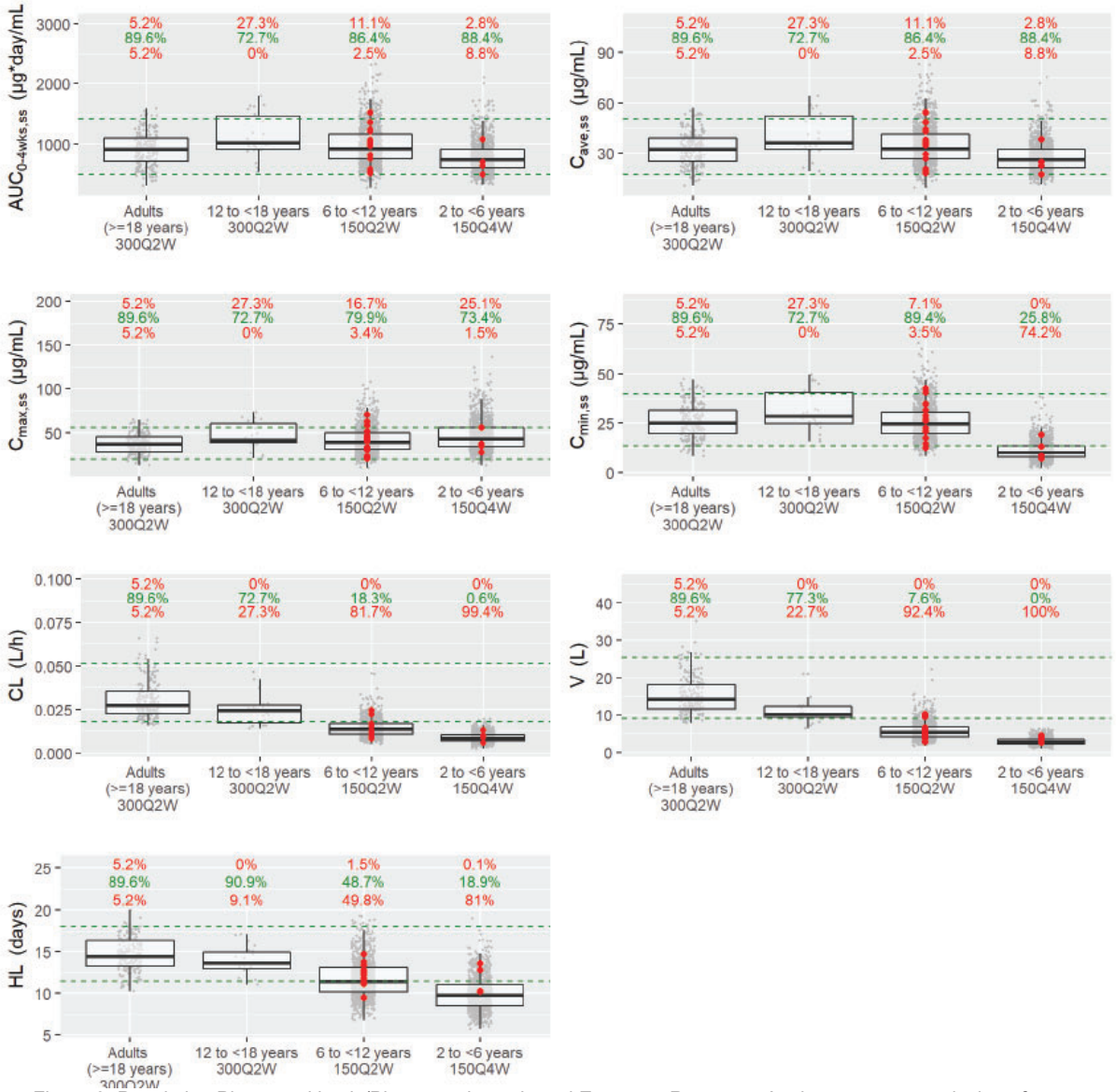


Source: Section 11.9, 11.11, 11.12, 11.13, 11.14 and 11.18 Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab SHP643 for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: ηCL: Random Effect on Clearance; ηKA: Random Effect on Absorption Rate; ηV: Random Effect on Central Volume of Distribution

In original submission of the supplement 10 dated 2022/08/05, simulations were performed in a virtual population of pediatric patients and posthoc PK parameters of lanadelumab were derived. The median (range) of body weight in patients 2 to <6 (N=1000) and 6 to <12 (N=1000) years were 15.7 (10.5 - 24.6) kg and 29.4 (17.5 – 52.7) kg, respectively. The proportion of exposure parameters in pediatric patients within the reference range in adults (≥18 years) from Study DX-2930-03 and -04 are presented in Figure 25. However, it was noted that the median C_{min} of 2-6 year old patients with 150 mg Q4W dosing is lower than the 5% lower limit of reference data (300 mg Q2W in adult), which may impact drug efficacy. An IR letter was sent to ask Applicant to comment on the potential impact on efficacy for 150Q4W dose and conduct simulation for alternative dosing regimens to optimize the dosing in 2-6 year old patients[2]. The Applicant submitted their response to the IR on 9/28/2022. In the response, the $C_{min,ss}$ of 2 to <6 year-old patients was further compared with the adults receiving 300 mg Q4W (Figure 26). The median $C_{min,ss}$ in 2 to <6 years old with 150 mg Q4W dose is ~23% higher than that associated with the 300 mg Q4W dose. Overall, the exposure of 150 mg Q4W in 2-6 year old patients falls between the exposure of the two approved dose regimens in adults and adolescents (i.e., 300 mg Q2W and 300 mg Q4W).

[2] DARRTS, BLA761090, Jackson, Colette C, 9/15/2022 COR-SBLAIR-01 (Pending BLA Information Request) Supplement 10 (Efficacy)

Figure 25. Comparison PK and Exposure Parameters of Lanadelumab Across Age Groups (Ref: 300 mg Q2W in Adults)

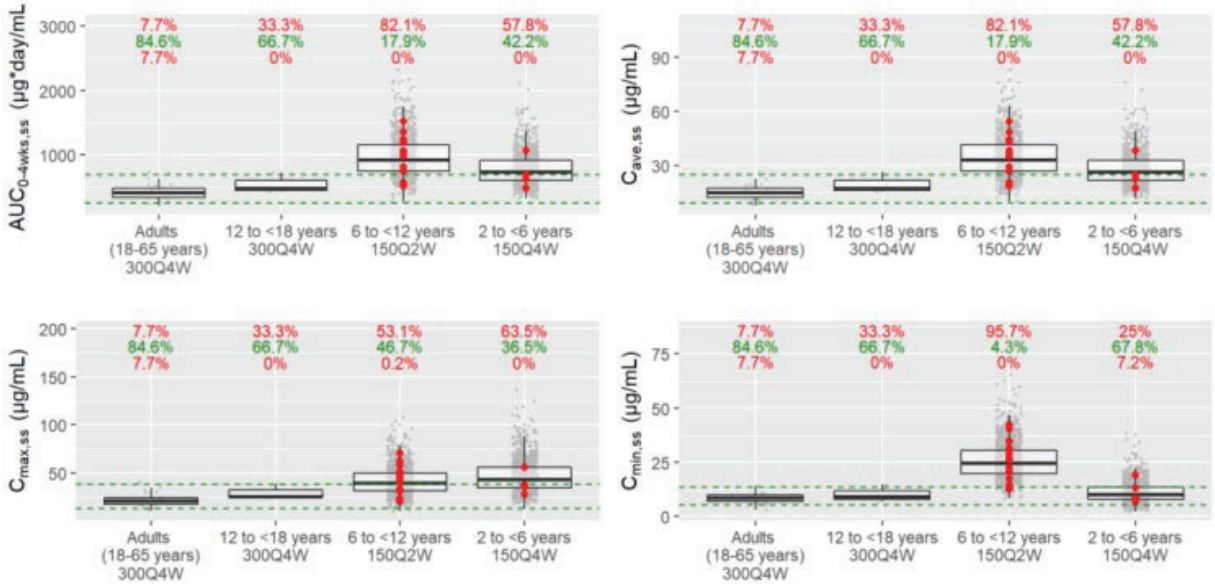


Source: Figure 9, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age

Note: the horizontal green dashed lines is the 5th and 95th percentiles of the reference data (i.e. 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; red circles represent the observed values in the SPRING trial

Abbreviations: AUC0-4weeks: area under the curve of 4 week; Cave,ss: average concentration at steady-state; Cmax,ss: maximum concentration at steady-state; Cmin,ss: minimum concentration at steady state; CL: apparent clearance; HL: half-life; Q2W: every two weeks, Q4W: every four weeks; V: apparent volume of distribution

Figure 26. Comparison PK and Exposure Parameters of Lanadelumab Across Age Groups (Ref: 300 mg Q4W in Adults)



Source: Figure 3, IR response 2022-09-28.
Note (1): boxplots for adults and adolescents are based on data from the actual subjects enrolled in Study DX-2930-03 and received 300 mg q4wks N=26 adults and 3 adolescents). Boxplots for pediatric patients 2 to <12 years are based on data from the simulated virtual subjects N=1000 in 6 to <12 years and N=1000 in 2 to <6 years; grey circles). Red circles laid over the boxplots of pediatric patients 2 to <12 years old represent the exposures based on the model-based post-hoc parameter estimates of the actual subjects enrolled in the SPRING trial (i.e., N=17 in 6 to <12 years and N=4 in 2 to <6 years).
Abbreviations: AUC0-4wks,ss: area under the curve of 4 weeks at steady state; Cavg,ss: average concentration at steady state; Cmax,ss: maximum concentration at steady state; Cmin,ss: minimum concentration at steady state; Q2W/q2wks: every 2 weeks, Q4W/q4wks: every 4 weeks

15.3.3.2. Exposure-Response (E-R) Analysis

15.3.3.2.1. Review Summary

In general, the Applicant's exposure-response (E-R) analysis is considered acceptable for the purpose of characterizing the E-R relationships of lanadelumab for efficacy and adverse events (AEs) on efficacy and safety in long-term prophylaxis against acute attacks of hereditary angioedema (HAE) in pediatric patients 2 to < 12 years of age. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

15.3.3.2.2. Methods

Safety and efficacy E-R analyses were performed for pediatric patients 2 to < 12 years of age. The exposures generated using the final population PK model were used for the following E-R analyses: 1) efficacy endpoint (the number of HAE attack per month, time to first HAE attack); and 2) safety endpoints (liver enzyme such as ALT, AST, and total bilirubin, activated partial thromboplastin time (aPTT) and international normalized ratio (INR), hematology indices such as erythrocyte count, platelet count and WBC, cardiac parameters such as diastolic blood pressure, heart rate and systolic blood pressure, and QTc parameters such as QTcB and QTcF.

15.3.3.2.3. Results

15.3.3.2.3.1. Efficacy

A longitudinal exposure-response model was constructed to simultaneously assess the impact of treatment duration and exposure-response relationship. The model that best characterized the relationship between lanadelumab exposure and the number of HAE attack per month included a placebo model (time-response model based on an exponential decay over time) and a drug effect model including an exponential exposure response model with a delay parameter. The following exposure parameters were tested: the lowest concentration over the monthly period (Cmin), the maximum concentration over the monthly period (Cmax), and the area under the curve over 4 weeks ($AUC_{0\text{-}4weeks}$). The model with $AUC_{0\text{-}4weeks}$ resulted in the lowest OFV. Age did not have an effect on any exposure-response parameters, which suggest that the exposure response is similar in adult and pediatric patients. The final longitudinal exposure-response model was described by the following lambda function:

$$\text{LAMBDA} = \text{INTERC} \times \text{BASE} \times e^{-\text{PLAC}\times\text{TIME}} \times e^{-\text{EFF}\times[1-e^{-\text{K}\times\text{TIME}}]}$$

Where LAMBDA = attack rate parameter (assuming Poisson distribution)

INTERC = intercept

BASE = scaling factor on INTERC which is dependent on the average monthly HAE attack rate at run-in.

PLAC = placebo effect

EFF = drug effect, described as an estimated slope x $AUC_{0\text{-}4weeks,i,j}$ which represent the $AUC_{0\text{-}4weeks}$ for individual i at month j. The shape of the relationship corresponds to an exponential decay since the slope x $AUC_{0\text{-}4weeks,i,j}$ is exponentiated as part of the EFF parameter.

K = Time varying effect of drug (Delay effect)

TIME = Month defined as a 28-day period. At Month 1, patients on lanadelumab received their first dose on Day 1. Month 1 to 40 are available in the current dataset.

Parameters derived with the final longitudinal exposure-response model of lanadelumab are listed in Table 23. The intercept is representative of the Monthly HAE attack at Month 1 which covers a 28-day period including lanadelumab exposure in patients who started dosing on Day 1. A visual predictive curve (VPC) was performed to confirm the predictive performance of the model in the SPRING trial and the results are listed in Figure 27. The shape of the exposure-response relationship for the number of HAE attacks from Month 1 to 6 in patients with a typical 2 HAE attack per month at baseline (run-in) is presented in Figure 28. Model-predicted median (90% prediction interval) number of HAE attack from Month 1 to 6 for the above median lanadelumab $AUC_{0\text{-}4weeks}$ values in patients 2 to <6 years (150 mg Q4W) and 6 to <12 (150 mg Q2W) with 2 HAE attack per month at baseline are presented in Table 24. Based on the exposure parameters in the SPRING trial, the median $AUC_{0\text{-}4weeks}$ in patients 2 to <6 years was 662 µg.day/mL and 1044 µg.day/mL for 150 mg Q4W and 150 mg Q2W, respectively. Thus, the

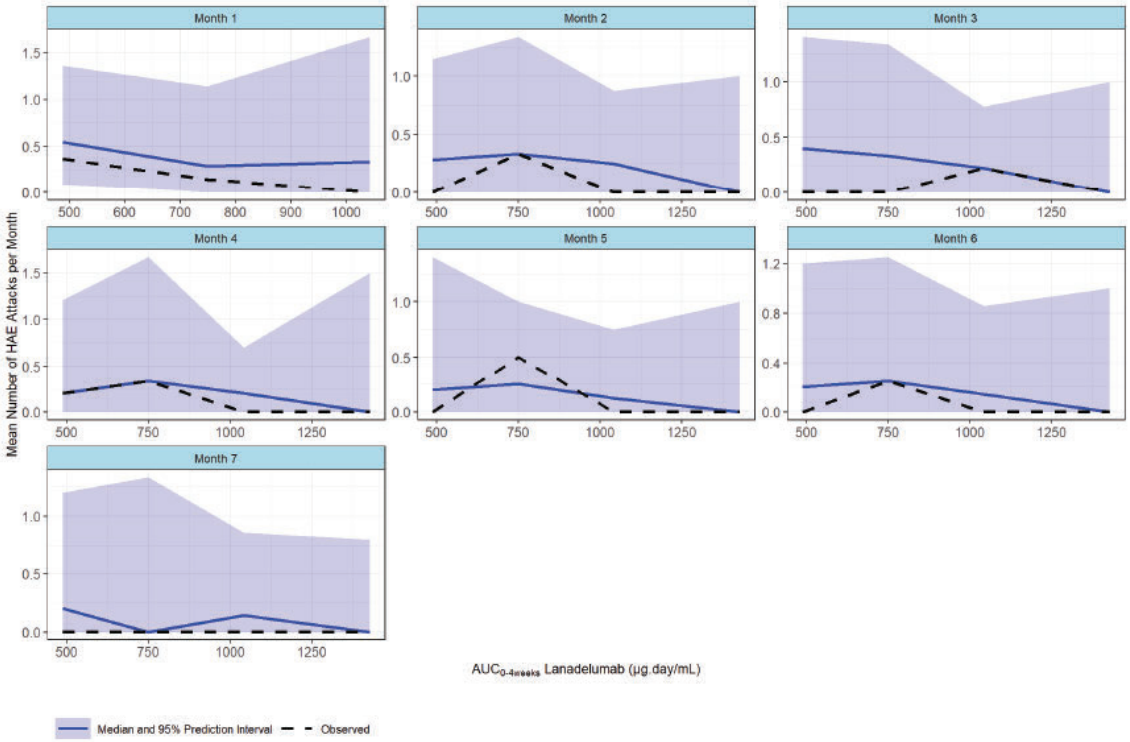
ER analysis confirmed that the current dosing regimen in patients 2 to <6 years (150 mg Q4W) and 6 to <12 years (150 mg Q2W) resulted in lanadelumab exposure associated with a reduction of HAE attack per month.

Table 23. Longitudinal Exposure-Response Model - Parameter Estimates

Parameters (Unit)	Typical Value	Bootstrap (n=500 replicates)		
		RSE%	Median (2.5% - 97.5% Percentile)	η Shrinkage (%)
Fixed Effect				
Intercept (Month 1)	0.863	15.0	0.867 (0.633 - 1.11)	-
Placebo Effect	0.0165	16.8	0.0168 (0.00824 - 0.0255)	-
Drug Effect Slope (1/µg*day/mL)	0.00158	26.8	0.00156 (0.00102 - 0.00208)	-
Drug Effect Delay ($month^{-1}$)	1.04	188	1.10 (0.519 - 2.95)	-
Covariate Effect				
HAE Attack Run-In on Intercept	x (HAE Attack Run-In/3)$^{0.563}$	20.8	0.559 (0.334 - 0.789)	-
Random Effects				
ω Intercept (Month 1)	0.894	10.5	0.882 (0.722 - 1.07)	30.0
ω Slope	0.954	8.58	0.945 (0.807 - 1.11)	27.3

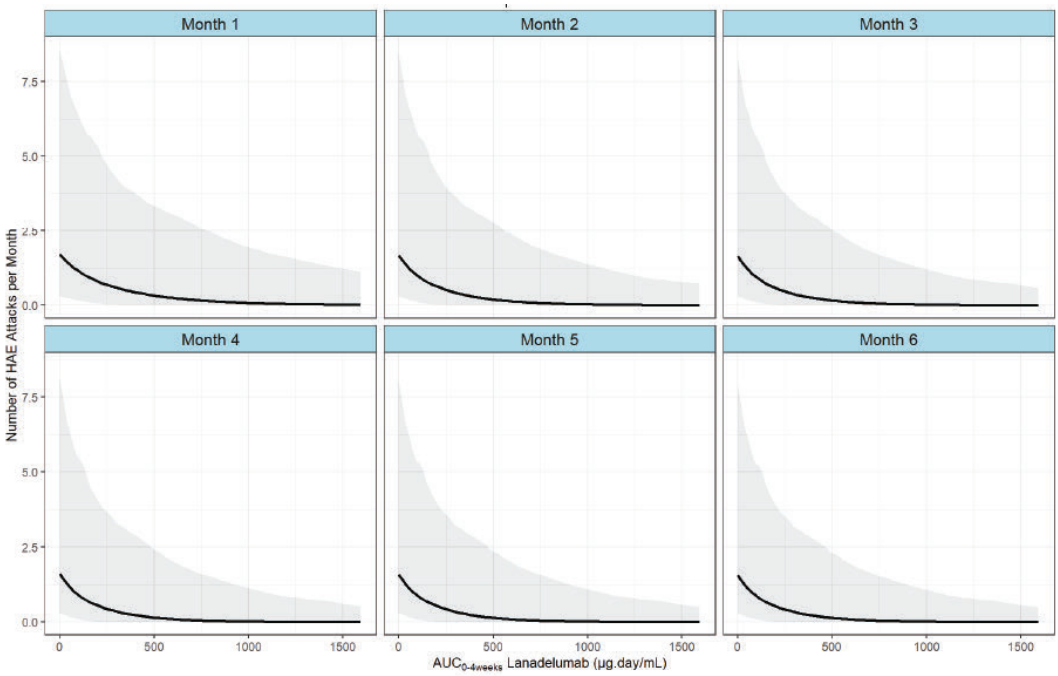
Source: Table 15, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Intercept = predicted average monthly HAE attack at Month 1; Placebo Effect = estimated placebo effect on average monthly HAE attack; Slope slope linking the AUC0-4weeks and the drug effect on average monthly HAE attack; Delay = first-order rate of the time effect for treatment effect on average monthly HAE attack;
Note: Of a total of 500 bootstrap runs, a total of 473 (94.6% runs successfully converged.
Abbreviations: NA: not applicable; RSE: relative standard error; IIV: interindividual variability; ω: omega, which represents the standard deviation of the between-subject variability.

Figure 27. VPC for the Longitudinal Exposure-Response Model for the Average Number of HAE Attacks Per Month – SPRING Trial



Source: Figure 17, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: HAE: hereditary angioedema; VPC: visual predictive curve

Figure 28. Exposure-Response Relationship From Month 1 to 6 in a Patient With 2 HAE Attack per Month at Baseline



Source: Figure 18, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Note: $AUC_{0\text{-}4weeks}$ corresponds to the area under the concentration-time curve over 4 weeks at Month 6. The black line represents the median number of HAE attack at Month 6 and the shaded is the 90% prediction interval.
Abbreviations: HAE: hereditary angioedema

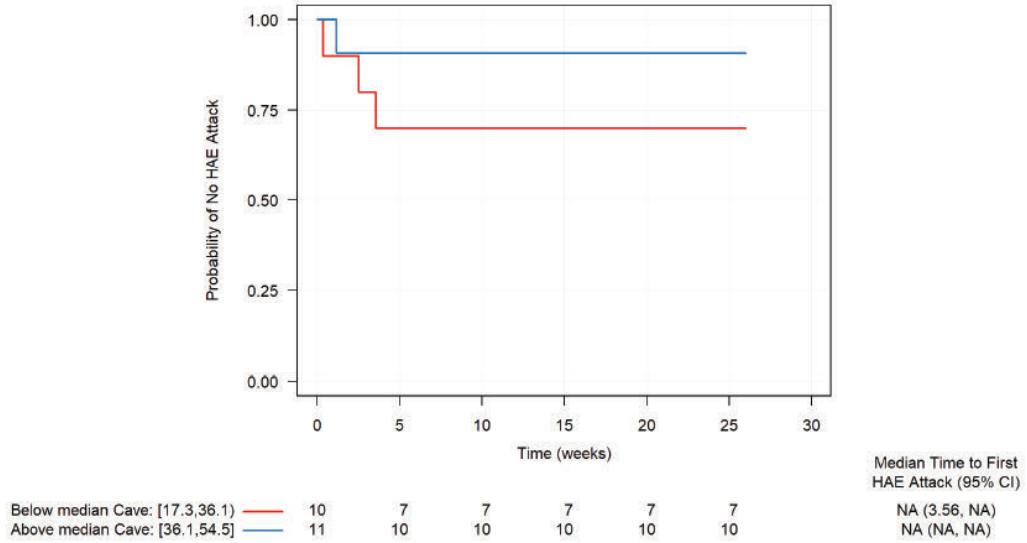
Table 24. Model-Predicted Median (90% PI) Number of HAE Attack From Month 1 to 6 in a Patient With 2 HAE Attack per Month at Baseline

Months	Model-Predicted Median (90% PI)		
	$AUC_{0\text{-}4weeks}$ = 0 µg.day/mL	$AUC_{0\text{-}4weeks}$ = 662 µg.day/mL	$AUC_{0\text{-}4weeks}$ = 1044 µg.day/mL
1	1.69 (0.31 – 8.56)	0.21 (0.00 – 2.89)	0.07 (0.00 – 1.87)
2	1.66 (0.30 – 8.42)	0.11 (0.00 - 2.15)	0.03 (0.00 - 1.30)
3	1.63 (0.30 – 8.28)	0.08 (0.00 – 1.90)	0.02 (0.00 - 1.13)
4	1.61 (0.29 – 8.14)	0.07 (0.00 – 1.83)	0.02 (0.00 - 1.06)
5	1.58 (0.29 – 8.01)	0.07 (0.00 – 1.79)	0.02 (0.00 - 1.03)
6	1.56 (0.28 – 7.88)	0.07 (0.00 – 1.75)	0.02 (0.00 – 1.00)

Source: Table 16, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: AUC: area under the concentration time curve; HAE: hereditary angioedema; PI: prediction interval

The Applicant also explored the time to first HAE attack was explored as a function of the $C_{ave,ss}$ of lanadelumab in pediatric subjects (SPRING trial) and non-pediatric subjects (DX-2930-03). Cox-proportional hazard regression models were developed for the probability of a first HAE attack based on $C_{ave,ss}$ and/or $C_{min,ss}$. $C_{ave,ss}$ was a better predictor than the $C_{min,ss}$ parameter based on AIC and is statistically significant ($p<0.001$). The effect of age was found to be not statistically significant ($p=0.409$). The probability of no HAE attacks vs. the $C_{ave,ss}$ in the SPRING trial (above and below median) are presented in Figure 29. The hazard ratio (HR) with 95% CI for a 1 µg/mL increment of $C_{ave,ss}$ was 0.943 (0.925 - 0.962).

Figure 29. Exposure-Response Relationship – Time to First HAE Attacks as a Function of Lanadelumab $C_{ave,ss}$ in the SPRING Trial



Source: Figure 19, Population Pharmacokinetic/Pharmacodynamic and Exposure-Response Analyses to support dosing of Lanadelumab (SHP643) for long-term Prophylaxis against acute attacks of hereditary angioedema in pediatric subjects 2 to <12 years of age.
Abbreviations: $C_{ave,\ ss}$: average plasma concentration at steady state; HAE: hereditary angioedema

15.3.3.2.3.2. Safety

Exposure-response analyses were performed to assess the relationship between lanadelumab exposure and the maximum change from baseline in liver enzyme, aPTT and international normalized ratio (INR), hematology indices, as well as cardiac and QTc parameters. The strength of the relationship was assessed using statistical estimator (r^2, slope, and p-value for slope of 0). A linear regression model was developed by including the effect of lanadelumab exposure ($C_{max,ss}$, $C_{min,ss}$, $C_{ave,ss}$). The effect of lanadelumab was deemed significant if a Spearman correlation >0.5 and a statistically significant ($p<0.05$) relationship was observed. A low correlation (<0.5) or lack of statistical significance ($p>0.05$) was observed between exposure parameters of lanadelumab and all the above safety endpoints.

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