

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761090Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

**NDA/BLA Multi-disciplinary Review and Evaluation**

<b>Application Type</b>	BLA
<b>Application Number(s)</b>	761090
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<b>Submit Date(s)</b>	December 26, 2017
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<b>PDUFA Goal Date</b>	August 24, 2018
<b>Division/Office</b>	DPARP/ODE II
<b>Review Completion Date</b>	August 22, 2018
<b>Established Name</b>	Lanadelumab
<b>(Proposed) Trade Name</b>	Takhzyro
<b>Pharmacologic Class</b>	Biologic
<b>Code name</b>	SHP643, DX-2930
<b>Applicant</b>	Dyax
<b>Formulation(s)</b>	Ready to use solution for injection
<b>Dosing Regimen</b>	300 mg every 2 weeks
<b>Applicant Proposed Indication(s)/Population(s)</b>	For prophylaxis to prevent attacks (b) (4) of hereditary angioedema (HAE) in patients 12 years and older.
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	For prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older

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OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management

## Glossary

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AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
C1-INH	C1-esterase inhibitor
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007

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FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HAE	hereditary angioedema
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LAN	Lanadelumab
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy

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SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

## 1 Executive Summary

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### 1.1. Product Introduction

Lanadelumab is a fully human monoclonal antibody (IgG1κ) targeting active plasma kallikrein for prophylaxis to prevent attacks of hereditary angioedema in patients 12 years and older. It is a new molecular entity not approved for use in any country. The dosing regimen for approval consists of a recommended starting dose of 300 mg subcutaneously (SC) every 2 weeks.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action for this application is Approval for subcutaneously administered lanadelumab 300 mg every 2 weeks (Q2W) for prophylaxis to prevent attacks of hereditary angioedema in patients 12 years and older. To support this application, the Applicant conducted a single 26-week, adequate, well-controlled pivotal efficacy and safety trial in adolescents and adults with Type I or II HAE. Results from this trial demonstrated substantial evidence of efficacy with all lanadelumab doses evaluated compared to placebo for the primary endpoint of monthly attack rate and for multiple supportive endpoints, such as rate of moderate to severe attacks, rate of attacks requiring rescue medication, and proportion of attack-free subjects. Although the numerically greater treatment effect in the high dose arm supports a recommended starting dose of 300 mg Q2W, the totality of data support providing an option in labeling to extend the dosing interval in some patients from every 2 to every 4 weeks after a period of (b) (4) 6 months while maintaining similar efficacy.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

Hereditary angioedema (HAE) is a rare, autosomal dominant, inherited condition characterized by intermittent, unpredictable attacks of angioedema. HAE is caused by mutations in the *SERPING1* gene, resulting in deficient or dysfunctional 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. Absence of functional C1-INH leads to dysregulation of the contact system, unchecked kallikrein activity, and ultimately widespread release of bradykinin which increases

vascular permeability causing the characteristic swelling of acute HAE attacks. Although the exact prevalence is unknown, 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.) and is categorized as an orphan disease. The 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 on the hands, feet, and face) can cause disabling pain and significant morbidity. These attacks are highly variable in frequency and location among individuals and even within a given individual.

The efficacy and safety of lanadelumab was evaluated in a single, well-controlled, adequately designed pivotal trial in Type I and II HAE patients 12 years of age and older. Lanadelumab treatment for 24 weeks versus placebo resulted in statistically significant and clinically meaningful reductions in monthly HAE attack rate, monthly rate of moderate to severe HAE attacks, and monthly rate of HAE attacks requiring acute rescue therapy with all doses/dosing regimens evaluated (300 mg Q2W, 300 mg Q4W, and 150 mg Q4W). Efficacy was further supported by additional endpoints such as proportion of attack-free patients and percentage of patients achieving pre-defined threshold reductions in attacks from baseline for all doses compared to placebo. Although the numerically greater treatment effect in the high dose arm supports a recommended starting dose of 300 mg Q2W, the totality of data support providing an option in labeling to extend the dosing interval in some patients from every 2 to every 4 weeks after a period of (b) (4) 6 months while maintaining similar efficacy. Allowing physicians and patients the flexibility to extend the dosing interval to individualize therapy.

The safety data submitted with the BLA was sufficient to assess the safety of lanadelumab in the proposed HAE population. Hypersensitivity reactions and transaminase elevations emerged as a potential safety signals. However, hypersensitivity reactions were mild and self-limited, and increases in AST/ALT were generally transient, asymptomatic, not dose-dependent, and/or confounded by underlying co-morbidities. Although abnormal bleeding/hypercoagulability events were identified as adverse events of special interest (AESIs) *a priori*, no events were reported. Injection site reactions mainly consisting of pain, bruising, or erythema were the most commonly reported adverse reactions, but were not dose-dependent or dose-limiting. No safety concerns were identified that should preclude approval or require a REMS. Efficacy and safety results across various demographic and baseline characteristic subgroups were generally consistent with the overall findings. Overall, the risk/benefit profile for lanadelumab in the treatment of a rare, serious disease such as HAE is favorable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Hereditary angioedema (HAE) is a rare, genetic condition caused by mutations in the <i>SERPING1</i> gene, resulting in deficiency or dysfunction of C1-esterase inhibitor (C1-INH) protein</li> </ul>	Hereditary angioedema is a rare, genetic, potentially life-threatening disease characterized by unpredictable, recurrent

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>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.</li> <li>Absence of functional C1-INH leads to characteristic swelling of acute HAE attacks.</li> <li>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.).</li> <li>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.</li> </ul>	<p>swelling attacks. HAE types included in the proposed indication represent most patients with HAE in the U.S.</p>
<p><a href="#"><u>Current Treatment Options</u></a></p>	<ul style="list-style-type: none"> <li>No cure exists; however, there are several approved therapies for prevention (i.e., prophylaxis) as well as treatment of acute attacks</li> <li>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.</li> <li>Prophylactic therapies do not eliminate all HAE attacks in all patients.</li> </ul>	<p>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.</p>
<p><a href="#"><u>Benefit</u></a></p>	<ul style="list-style-type: none"> <li>The Applicant has demonstrated substantial evidence of efficacy for lanadelumab in Type I and II HAE patients based on reductions in monthly HAE attack rate, monthly rate of moderate to severe HAE attacks, and monthly rate of HAE attacks requiring acute rescue</li> </ul>	<p>Lanadelumab provides clinically relevant treatment benefits through reduction or prevention of attacks in HAE patients. All doses studied were effective compared to</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>therapy.</p> <ul style="list-style-type: none"> <li>All doses of lanadelumab (300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks) were effective compared to placebo</li> <li>The largest treatment effect was seen with the highest dose of lanadelumab; therefore, 300 mg every 2 weeks is the recommended starting dose</li> <li>Titrating the dose up or down was not formally evaluated in the study</li> <li>Post-hoc analyses of available data from the placebo controlled trial and open-label extension study suggest that the dosing interval may be extended beyond every 2 weeks without loss of efficacy</li> <li>Interpretation of post-hoc analyses is limited by small sample sizes, unblinded treatment and high degree of inter-patient variability in disease severity</li> </ul>	<p>placebo; however, the highest dose of 300 mg every 2 weeks was most effective and is the recommended starting dose. Extending the dosing interval from every 2 to every 4 weeks after a period of (b) (4) 6 months can be considered an option for some patients to add flexibility for individualization of therapy.</p>
<p><a href="#">Risk and Risk Management</a></p>	<ul style="list-style-type: none"> <li>The safety program for lanadelumab identified potential risks for injection site reactions, hypersensitivity, and elevated liver function tests</li> <li>No dose-related adverse reactions were observed</li> <li>No REMS is proposed</li> </ul>	<p>No substantial safety findings were identified in clinical trials that outweigh the potential benefit. Potential risks of injection site reactions, hypersensitivity and abnormal liver function tests can be managed through labeling and routine pharmacovigilance.</p>

#### 1.4. Patient Experience Data

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

<input type="checkbox"/>	<p>The patient experience data that was submitted as part of the application, include:</p>	<p>Section where discussed, if applicable</p>
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	X	Clinical outcome assessment (COA) data, such as	
		<input checked="" type="checkbox"/> Patient reported outcome (PRO)	Sections 8.1.1 and 8.1.1.1
		<input type="checkbox"/> Observer reported outcome (ObsRO)	
		<input type="checkbox"/> Clinician reported outcome (ClinRO)	
		<input type="checkbox"/> Performance outcome (PerfO)	
		<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	X	Patient-focused drug development or other stakeholder meeting summary reports	Not submitted to BLA but discussed in Section 2.1 Analysis of Condition
		<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
		<input type="checkbox"/> Natural history studies	
		<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
		<input type="checkbox"/> Other: (Please specify)	
X		Patient experience data that was not submitted in the application, but was considered in this review.	Section 2.1 – HAE PFDD workshop, Voice of the Patient report

X Stacy Chin, M.D. (e-signature at end of document)

Cross-Disciplinary Team Leader

## 2 Therapeutic Context

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### 2.1. Analysis of Condition

Hereditary angioedema (HAE) is a rare, autosomal dominant, inherited condition characterized by intermittent, unpredictable attacks of angioedema.<sup>1</sup> 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. 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.

Figure 1 provides a more detailed representation of how C1-INH functions within the contact system. C1-INH is an endogenous inhibitor of the serine protease enzymes Factor XIIa and plasma kallikrein. Factor XIIa converts pre-kallikrein to active plasma kallikrein, which in turn cleaves high molecular weight kininogen (HMWK) to form bradykinin and cleaved HMWK (cHMWK). Bradykinin is a polypeptide signaling molecule that participates in multiple biological functions including blood coagulation, activation of inflammation, and regulation of blood pressure.

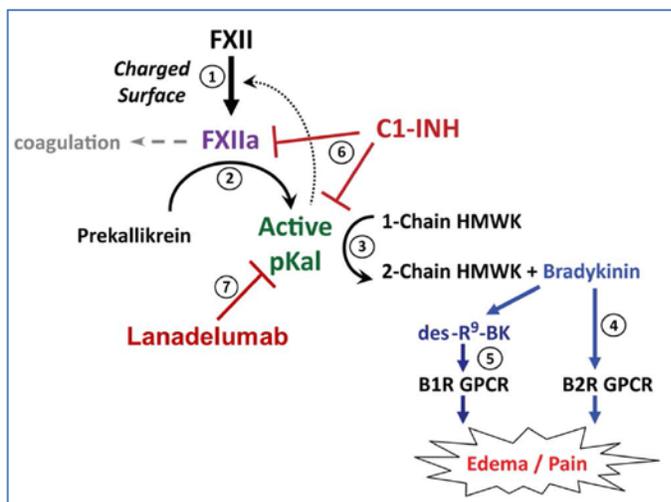
Patients with HAE have uncontrolled plasma kallikrein production and pathologic levels of bradykinin. The key triggering events that initiate an HAE attack are not completely understood<sup>2</sup>. Bradykinin activation of bradykinin B2 receptors at the surface of endothelial cells leads to vasodilation and decreased blood pressure. B2 activation also results in the vascular leakage and subsequent tissue swelling observed in HAE attacks. Bradykinin is converted to des-Arg<sup>9</sup> bradykinin in the plasma by carboxypeptidase N. des-Arg<sup>9</sup> bradykinin activates bradykinin B1 receptors, also contributing to symptoms of HAE. Lanadelumab is designed to block the enzymatic function of plasma kallikrein and prevent the proteolytic conversion of HMWK to bradykinin.

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<sup>1</sup> Zuraw BL et al. *J Allergy Clin Immunol* 2013; 131 (6):1491-3

<sup>2</sup> Kenniston et al. (2014) Inhibition of plasma kallikrein by a highly specific active site blocking antibody. *The Journal of Biological Chemistry*. 289, 23596 – 23608.

Figure 1. Contact (aka plasma kallikrein – kinin) system



Source: DX-2930 carcinogenicity assessment document

Although the exact prevalence is unknown, 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.) and is categorized as an orphan disease. Despite the autosomal dominant inheritance pattern, roughly a quarter of patients have spontaneous mutations, and diagnosis is often delayed by several years. The age at which attacks begin is variable, but symptoms during infancy are exceedingly rare. Based on literature reports, the median age of symptom onset is between 6 and 11 years of age with attack frequency increasing after puberty and continuing throughout an individual's life. The 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, hands, feet, and face) can cause disabling pain and significant morbidity. These attacks are highly variable in frequency and location among individuals and even within a given individual. If untreated, attacks may occur on average every 1-2 weeks and typically last 48 to 72 hours. Current therapies used by patients with HAE to help manage their disease are listed in Section 2.2.

The Agency convened a Patient-Focused Drug Development public meeting for hereditary angioedema on September 25, 2017, during which the FDA heard directly from patients, families and caregivers about their experiences with HAE attacks and the life-changing impact of available therapies. Approximately 110 patients with HAE and their representatives were present at the meeting while 52 participants joined through live webcast. The meeting discussion focused on two key topics: 1) disease symptoms and daily impacts that matter most to patients and caregivers and 2) patients' perspectives on current approaches to treating HAE and on participating in clinical studies. The Voice of the Patient report highlighted the following overarching themes from the meeting discussion:

- Diagnostic delays and lack of awareness about HAE disease and recognition of signs/symptoms by healthcare providers

- Unpredictability of attacks
- Pain, disability, and disfigurement that occurs with attacks
- Emotional stress that accompanies the condition
- Impact on work, family, and social life
- Life-changing effect of newer approved treatments
- Unmet need for treatments that are less invasive, improve predictability of attacks, have fewer side effects, and ultimately lead to cure
- Areas for future research include hormonal influences on the disease, therapies for children, and therapies for HAE types that are less responsive to currently available therapies
- Willingness to participate in clinical trials as well as natural history studies

## 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 below, fresh frozen plasma (FFP) and antifibrinolytics (tranexamic acid,  $\epsilon$ -aminocaproic acid) are available for HAE prophylaxis; however, with availability of more effective 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
<b>FDA Approved Treatments for Prophylaxis</b>					
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 q3-4 days	thromboembolism hypersensitivity transmissible infection	≥ 6 years
Haegarda	plasma derived C1-INH	2017	60 IU/kg SC q3-4 days	same as Cinryze	adolescents
<b>FDA Approved Treatments for Acute Attacks</b>					
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)		≥ 18 years
Ruconest	recombinant C1-INH	2014	50 units/kg IV (max 4200 U/dose)	thromboembolism hypersensitivity	adolescents
Source: <a href="mailto:Drugs@FDA.gov">Drugs@FDA.gov</a> ( <a href="https://www.accessdata.fda.gov/scripts/cder/daf/">https://www.accessdata.fda.gov/scripts/cder/daf/</a> )					

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Lanadelumab is not approved or marketed in the U.S. or any foreign country for any other indications.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

Lanadelumab (also referred to as DX-2930) was developed under IND 116,647, which was opened on 7/25/13. Lanadelumab was granted orphan therapy designation on 11/26/13, fast track designation on 3/11/15, breakthrough therapy designation on 7/2/15, and priority review designation on 2/22/18. 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.

*January 16, 2013: Pre-IND meeting*



*March 20, 2015: Type C meeting*

- FDA emphasized the need to justify the target population intended to receive life-long therapy with a mAb
- Dosing intervals other than every 2 weeks should be explored. Based on the limited clinical data, the half-life and therapeutic effects of DX-2930 appear to be longer than 2 weeks.
- FDA raised potential ethical concerns about discontinuing effective prophylactic therapies for enrollment
- The proposed study with a 3-month treatment duration is too short to support a BLA and would be considered a proof of concept study.
- At least 1 year of safety data will be needed to support a BLA for a new mAb intended for chronic use.
- General agreement with the Sponsor's proposed efficacy endpoints
- The clinical relevance of plasma kallikrein inhibition is uncertain since it has not been directly linked to the clinical outcome of interest, i.e., a reduction in acute HAE attacks.

*June 30, 2015: EOP2 meeting*

- FDA informed the Sponsor of forthcoming breakthrough therapy designation
- Main deficiency in proposed clinical program is inadequate exploration and

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characterization of the dosing interval. FDA anticipates that a range of dosing intervals may be included in the label to suit different patient needs since HAE is a highly variable disease

- Discussed alternative study designs to obtain sufficient data regarding the nominal dose and dosing frequency
- Strategy for enrolling patients with minimum attack rate and washing out prophylactic therapies is reasonable. Adolescent patients may be included, but should not be required to discontinue prophylactic medications to enter the study
- Agreement with HAE attack definition

*September 4, 2015: Type B meeting*

- Discussed revised phase 3 protocol and use of the OLE study to characterize the outer bounds of dosing frequency

*April 24, 2016: Written responses*

- Recommended evaluating >50 patients for self-administration and allowing patients to self-administer study drug throughout the OLE

*January 13, 2017: Type B meeting, WRO*

- A complete package is required at submission, which includes 12 months of safety data for all patients who enrolled in Study DX-2930-03 and rolled over into Study DX-2930-04
- To obtain a pediatric indication in younger patients, must ensure adequate representation across the entire age range being sought. (b) (4)
- No dedicated PK study required for transitioning from a vial to (b) (4) if the formulation is identical

*August 22, 2017: pre-BLA preliminary responses*

- Agreement with plan for BLA submission

*September 1, 2017: pre-BLA t-con*

- CMC data for (b) (4) 300 mg presentations should be included in the BLA submission. Expect the proposed label to include information regarding all doses/dosing regimens

*October 31, 2017: pre-submission initiated*

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

The pivotal efficacy and safety trial, DX2930-03, in the lanadelumab development program was a multicenter trial with each site enrolling a small number of subjects. Therefore, the potential for any individual study center to impact the efficacy and safety findings was limited. Two clinical sites (Dr. Anderson/Site #101 and Dr. Craig/Site #106) were selected for inspection for trial DX-2930-03. OSI reports for these sites found the study data reliable in support of the requested indication.

### 4.2. Product Quality

Lanadelumab is a fully human IgG1/ $\kappa$ -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 (b) (4) 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. Inspection of manufacturing facilities concluded NAI. The OPQ review of this application recommends approval. Refer to the separate product quality reviews for additional details.

### 4.3. Clinical Microbiology

From a microbial control and microbiology product quality perspective, the lanadelumab drug substance and Takhzyro drug product are approvable. During the review cycle, the Agency sent multiple IRs to the Applicant regarding methods for (b) (4), (b) (4), bioburden and endotoxin controls. The Applicant provided adequate responses to the information requests. However, the low endotoxin recovery (LER) study submitted to the original BLA (RL-REPORT-06486) did not support the claimed hold time for (b) (4) of (b) (4) hours, so the Agency requested that the LER study be repeated during the review cycle. While results submitted from the repeat LER study showed no LER observed after a (b) (4) hold at (b) (4) °C, this did not represent the worst-case scenario for temperature (b) (4). Therefore, a repeat LER study (b) (4) will be conducted as a postmarketing commitment (PMC). In addition, the Agency requested that the Applicant remove (b) (4) on stability, which is not a regulatory requirement (sterility testing only required at

release for each lot of drug product); the Applicant complied with the request. Refer to the drug substance and drug product microbiology reviews for additional details.

#### 4.4. **Devices and Companion Diagnostic Issues**

Not applicable

## 5 **Nonclinical Pharmacology/Toxicology**

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### 5.1. **Executive Summary**

#### *Introduction*

The Applicant has submitted a complete nonclinical pharmacology and toxicology program for lanadelumab. BLA 761090 is recommended for approval from the nonclinical pharmacology and toxicology perspective. There are no outstanding nonclinical issues.

#### *Brief Discussion of Nonclinical Findings*

The completed nonclinical studies support the approval of 300 mg DX-2930 as proposed in labeling as an SC therapy for the chronic, prophylactic treatment of hereditary angioedema.

The current review includes a detailed evaluation of the relevant nonclinical Pharmacology and Pharmacokinetics/ADME studies. The results of 4-week general toxicology studies in rats and monkeys are summarized. Complete reviews of the pivotal 39-week general toxicology study in monkeys, 13-week fertility study in male and female monkeys, and an enhanced pre- and postnatal development (ePPND) toxicology study conducted in monkeys are included along with a review of the Applicant's carcinogenicity assessment for DX-2930.

DX-2930 inhibited human plasma kallikrein function in a cell-free system with a potency of 125 pM. Comparable inhibitory potencies were observed with rat and monkey plasma kallikrein. In vivo efficacy was demonstrated with DX-2930 doses  $\geq 1$  mg/kg (SC) in the rat carrageenan-induced paw edema model.

The most appropriate Established Pharmacologic Classification (EPC) for DX-2930 is "plasma kallikrein inhibitor", identical to the EPC used for Kalbitor (ecallantide), the approved peptide inhibitor of plasma kallikrein.

Rats and monkeys were chosen by the Applicant as the species to be used in their in vivo nonclinical development program. DX-2930 is absorbed slowly after subcutaneous injection in humans and nonclinical species ( $T_{max}$ : 1 – 4 days), consistent with absorption of other approved SC therapeutic monoclonal antibodies. SC bioavailability was 66% in cynomolgus monkeys. DX-2930 distribution was confined to the blood volume in monkeys. In the ePPND study, DX-2930 crossed the blood-placenta barrier and was also detected in the milk of lactating monkeys. DX-

2930  $T_{1/2}$  was approximately 14 days in humans and 10 days in monkeys. Both values are consistent with expected values for therapeutic IgG1 mAbs.

DX-2930 was highly immunogenic in rats as evidenced by the development of neutralizing anti-drug antibodies (ADA) in nearly all treated animals in a 4-week SC toxicity study. A chronic toxicology study in rats was not considered feasible. A 39-week SC study in cynomolgus monkeys (once weekly dosing) represented the pivotal toxicology study to support marketing approval of DX-2930. No dose-limiting toxicities were identified. The target organs of toxicity were SC injection sites, although these findings were considered monitorable in a clinical setting. The mean  $AUC_{last}$  at the no observed adverse effect level (NOAEL) of 50 mg/kg was 110,500  $\mu\text{g}\cdot\text{hr}/\text{ml}$ . This exposure supports the clinical DX-2930 exposure at the maximum recommended human dose (MRHD) of 300 mg every 2 weeks.

The conduct of carcinogenicity studies in rodents was not feasible based on the development of ADA in SD rats after repeated dosing. Based on the results of the 39-week study in monkeys as well as evidence from the available scientific literature, chronic inhibition of bradykinin production via DX-2930 treatment is unlikely to affect carcinogenic risk in HAE patients.

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. Parameters evaluated included: Female menstrual cycle length; Male testicular volume, sperm motility & morphology, and spermatogenic staging. Histopathologic assessment of male and female reproductive organs identified no adverse findings. The NOAEL in this study was identified at 50 mg/kg.

In an enhanced pre- and post-natal development study, pregnant female cynomolgus monkeys were treated with 10 mg/kg or 50 mg/kg DX-2930 (SC) once per week from GD 20 – 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. The maternal NOAEL and the fetal/developmental NOAEL in this study were both defined at 50 mg/kg.

## 5.2. Referenced NDAs, BLAs, DMFs

- IND 116647: DX-2930 for the treatment of hereditary angioedema
  - All nonclinical studies in support of approval of BLA 761090 were conducted under IND 116647

## 5.3. Pharmacology

### *Kallikreins*

Kallikreins are serine protease enzymes. Mammals possess two major classes of kallikrein enzymes: *Plasma* kallikrein (KLKB1) and the *tissue* kallikrein family (KLK1 – KLK15). Plasma

kallikrein (abbreviated pKal) is the therapeutic target of DX-2930. DX-2930 has been shown to bind to pKal in a manner that fully occludes the pKal active site<sup>2</sup>.

Plasma kallikrein (pKal) is synthesized in the liver and circulates in the plasma as an inactive precursor (prekallikrein), which undergoes proteolytic cleavage by Factor XIIa to become activated<sup>3</sup>. The total amount of circulating prekallikrein is approximately 500 nM<sup>4</sup>. Human plasma kallikrein is 638 amino acids long and contains a trypsin-like protease domain in its C-terminus as well as 4 tandem repeats of 90 – 91 amino acids called APPLE domains in its N-terminus.

Tissue kallikreins are expressed throughout the entire body in humans and have varied functions. These proteins have an average length of approximately 260 amino acids, and are comprised of a trypsin-like protease domain only. Tissue kallikreins cleave low molecular weight kininogen to release lysyl-bradykinin<sup>3</sup>.

#### *Plasma kallikrein*

Once activated by Factor XII, pKal cleaves HMWK to form bradykinin and cHMWK. Bradykinin activation of Bradykinin B2 receptors at the surface of endothelial cells leads to vasodilation and decreased blood pressure. B2 activation also results in the vascular leakage and subsequent tissue swelling observed in HAE. The therapeutic action of DX-2930 in HAE patients involves inhibition of pKal to limit the generation of bradykinin from high molecular weight kininogen. Bradykinin has a short half-life in vivo (< 30 seconds) and is difficult to detect in biological samples. cHMWK is more readily measured and is used as an indirect indicator of pKal function.

Activated pKal has functional roles in biological processes beyond cleavage of HMWK, including the initiation of endothelial surface-mediated activation of coagulation. pKal also has a role in fibrinolysis, as it has been shown to be capable of cleaving plasminogen to plasmin. pKal functions less efficiently than tissue-type plasminogen activator (tPA) or urokinase-type plasminogen activator<sup>5</sup>. pKal activity is also associated with the initiation of the classical complement cascade pathway via activation of the C1 complex<sup>2</sup>. These functions of pKal are described here to indicate potential consequences of pKal inhibition by DX-2930 beyond the expected reduction in bradykinin production. It is noted that toxicology studies with DX-2930 did not indicate any disorders of blood coagulation, fibrinolysis, or inflammation.

### **Primary pharmacology**

#### *DX-2930 potency (in vitro, ex vivo)*

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<sup>3</sup> Koumandou, V. and A. Scorilas (2013) Evolution of the Plasma and Tissue Kallikreins, and their Alternative Splicing Isoforms. *PLoS One*. 8, e68074.

<sup>4</sup> Silverberg et al. (1995) The Contact System and its Disorders. In: *Blood: Principles and Practice of Hematology*. Handin, R. et al (editors). J.B. Lippincott Company. Philadelphia, 1127 – 1150.

<sup>5</sup> Bryant, J. and Shariat-Madar, Z. (2009). Human plasma-kallikrein system: Physiological and biochemical parameters. *Cardiovasc Hematol Agents Med Chem*. 7, 234 – 250.

- DX-2930 inhibits human, rat, and cynomolgus monkey pKal activity with comparable potencies (Table 2). Rats and cynomolgus monkeys are pharmacologically relevant species.

**Table 2. Summary of relevant studies of DX-2930 potency for inhibition of pKal function.**

Study	Model/ species	Design	Result
DRD-910-046*	In vitro: Human	DX-2930: In vitro inhibition of human plasma kallikrein cleavage of HMWK to form bradykinin [Bradykinin quantified by commercial bradykinin ELISA]	<u>K<sub>i</sub></u> = 125 pM
Notebooks 2857-074*, 2861*, 2827*	In vitro: Rat, mouse, rabbit, cyno	DX-2930: In vitro inhibition of plasma kallikrein cleavage of synthetic kallikrein substrate (Pro-Phe-Arg-AMC) [Cleavage quantified by measurement of AMC fluorescence]	<u>K<sub>i</sub></u> (pM) Rat: 170 Mouse: 300 Cynomolgus: 69 Rabbit: 14,400
Notebook 2857*	Ex vivo: human plasma	DX-2930: Inhibition of High molecular weight kininogen (HMWK) cleavage in kaolin or dextran-sulfate activated (contact system activated) human plasma [evaluated by Western blot analysis]	<u>DX-2930 concentration required to inhibit HMWK cleavage:</u> Kaolin: 400 nM Dextran sulfate: 80 nM
DRD-910-056 (Samples from (b) (4) 446029)	Ex vivo: Rat plasma	*Single dose of 25 or 50 mg/kg SC DX-2930 *Plasma samples taken 4 days later *Measure inhibition of HMWK cleavage in dextran-sulfate activated plasma [evaluated by Western blot analysis]	*HMWK cleavage was inhibited at both 25 & 50 mg/kg doses
DRD-910-056 (Samples from (b) (4) 446030)	Ex vivo: Cyno plasma	*Single dose of 25 or 50 mg/kg SC DX-2930 *Plasma samples taken 2 or 28 days later *Measure inhibition of HMWK cleavage in kaolin-activated plasma [evaluated by Western blot analysis]	*HMWK cleavage was inhibited at both 25 & 50 mg/kg doses
* Study is described in detail in Document DRD-910-045			

*DX-2930 binding specificity (in vitro)*

- DX-2930 binds active pKal, but not its precursor prekallikrein.
- DX-2930 can bind to free pKal as well as pKal that is complexed to HMWK at the endothelial cell surface.

**Table 3. Summary of relevant studies describing DX-2930 binding specificity**

Study	Model/ species	Design	Result
Notebook 2827-061*	Biacore Surface Plasmon Resonance (SPR)	*DX-2930 captured onto Biacore sensor chip surface via an anti-Fc antibody *Free pKal (500 nM) or Prekallikrein (500 nM) flowed over the surface of chip	*DX-2930 binds pKal *DX-2930 <u>does not</u> bind prekallikrein
Notebook 2827-013*	Biacore SPR	*2-chain HMWK was immobilized on Biacore sensor chip surface *DX-2930 pre-incubated with pKal *DX-2930: pKal complex was flowed over the surface of chip.	*DX-2930: pKal complex binds HMWK
Notebook 2827*	Human umbilical vein endothelial cells (HUVECs) grown on 96-well titer plates.	*HMWK was added to the HUVECs, followed by pKal, and then biotinylated DX-2930.  *DX2930 bound to pKal was visualized using streptavidin-alkaline phosphatase – p-nitrophenyl phosphate colorimetric methods	*DX-2930 can bind to active pKal that is assembled in a complex on the endothelial cell surface in HUVECs  * <u>Note</u> : functional studies to evaluate DX-2930 inhibition of pKal cleavage of HMWK were not conducted in this experimental system
* Study is described in detail in Document DRD-910-045			

### *DX-2930 efficacy (in vivo)*

#### Evaluation of anti-inflammatory activity of test material in a carrageenan paw edema (rat) model (Study R8048M-SHP643)

- DX-2930 (0, 1, 3, 10, 30 mg/kg) was administered SC in a single dose 24 h prior to injection of 0.1 ml 1% carrageenan into the right hind paw of rats. Indomethacin (5 mg/kg) was used as the positive control.
- DX-2930 demonstrated dose-dependent anti-inflammatory activity in this model (decreased paw volume relative to control) at doses  $\geq$  1 mg/kg.

### **Secondary pharmacology**

#### Tissue Cross Reactivity Study with human tissues (Study P2930-12-01)

- Apparent DX-2930-specific staining (min – mild) was observed in the cytoplasm of endothelial cells in multiple tissues. Cytoplasmic staining was also detected in neurons of the cerebellum, cerebral cortex, and eye.
- Evidence for cytoplasmic staining of DX-2930 is of limited toxicological significance given that this molecule will not have access to the cytoplasmic compartment in vivo due to its large size (~146 kDa).
- The study did not identify any potential off-target tissues of concern for DX-2930
- There was no evidence for specific DX-2930 staining in blood samples
- Positive and negative control samples provided the expected results, supporting the validity of the experimental methods.

*DX-2930 Effector function*

- DX-2930 binding affinity for human FcγRs and complement C1q was evaluated using Biacore SPR techniques. DX-2930 bound to FcγRs with Kd values consistent with expected values for IgG1 molecules (nM for FcγRI, μM for all others)<sup>6</sup>.
  - There was no evidence for increased binding affinity of DX-2930 for any of the FcγRs or C1q relative to reported values for other approved therapeutic mAbs (Study DRD-910-063).
- pKal is not a cell-surface protein. However, pKal complexed to HMWK can bind endothelial cell surfaces via interactions between domains in HMWK and cell surface proteins. Shire demonstrated that DX-2930 binds to pKal that is complexed to the endothelial cell surface (Study DRD-910-045). Under these conditions, the Fc region of the DX-2930 molecule could potentially evoke Fc receptor mediated effects.
- Therefore, Shire tested the ability of DX-2930 to evoke antibody dependent cell-mediated cytotoxicity (ADCC) or complement mediated cytotoxicity (CDC) using a human umbilical vein endothelial cell (HUVEC) model (Table 4).
  - There was no evidence for DX-2930 evoked ADCC or CDC in this model (Study DRD-910-065).

**Table 4. Summary of studies conducted to evaluate the potential for DX-2930 to evoke effector function.**

Study	Model/species	Design	Result
DRD-910-065*	*HUVECs + human NK cells (ADCC)  *HUVECs + rabbit complement (CDC)	*HUVECs grown on 96-well plates were the target cells *HMWK, then pKal was added to cells to form complex at cell surface *DX-2930 added to cells at 3, 6, 12, 60 μg/ml *ADCC induced by adding human NK cells from 3 different donors *CDC induced by adding rabbit complement *Cell lysis quantified by measuring release of the intracellular enzyme GAPDH using a bioluminescent substrate (aCella-TOX).	*There was no evidence for DX-2930 evoked ADCC or CDC
* Study is described in detail in Document DRD-910-045			

**Safety pharmacology**

*Electrocardiography*

Studies <sup>(b) (4)</sup> 446032 & <sup>(b) (4)</sup> 446033: 4-week and 6-month SC toxicity studies in cynomolgus monkeys

ECG data was collected by Jacketed External Telemetry in the 4-week and 6-month SC monkey toxicity studies. There was no evidence for DX-2930-related effects on ECG parameters

<sup>6</sup> Nimmerjahn, F. and Ravetch, J. (2008) Fcγ receptors as regulators of immune responses. *Nature Reviews Immunology*. 8, 34 - 47.

including heart rate in either study at doses up to 50 mg/kg/week (See nonclinical reviews dated 7/7/13 and 3/12/15).

#### *Central Nervous System*

##### Study (b) (4) 446031: 4-week SC toxicity study in SD rats

CNS endpoints were evaluated in the Functional Observational Battery (conducted at weeks 1 & 4) included in the 4-week SC toxicity study in rats. There was no effect of DX-2930 at up to 50 mg/kg/week (see nonclinical review dated 7/7/13).

#### *Respiratory system*

##### Study (b) (4) 446031: 4-week SC toxicity study in SD rats

Respiratory rate and respiratory character were assessed by technicians as part of the handling observations of the Functional Observational Battery (conducted at weeks 1 & 4) in the 4-week SC toxicity study in rats (Study (b) (4) 446031). Respiratory rate and respiratory character were judged to be normal by the testing technicians in all animals (doses up to 50 mg/kg/week) at both time points.

##### Study (b) (4) 446051: 4-week IV toxicity study in cynomolgus monkeys

- Male and female cynomolgus monkeys were dosed at 0, 5, 25, and 50 mg/kg IV once-weekly in this study. Blood pressure parameters and mean respiratory rate were measured in all animals at the following time points: Day -14/16, Day 3, Day 8, Day 15, Day 22, and Day 29.
- There was no evidence for effects of DX-2930 on any blood pressure parameter or on mean respiratory rate at up to 50 mg/kg/week (IV)
- DX-2930 mean  $C_{max}$  at the HD of 50 mg/kg/wk was 60-fold higher than the clinical  $C_{max}$  at the dose of 300 mg SC (1640 µg/ml vs. 27.5 µg/ml)

## 5.4. ADME/PK

Relevant ADME/TK data from studies conducted in humans, cynomolgus monkeys and SD rats is summarized in Table 5 below.

#### *Absorption*

- DX-2930  $T_{max}$  values were comparable between monkeys and humans after SC dosing.
  - $T_{max}$  values ranged from approximately 2.5 – 3.7 days.
- Subcutaneous bioavailability of DX-2930 was determined to be 66% in male cynomolgus monkeys (Study (b) (4) 446027). This is generally consistent with bioavailability values reported for approved SC therapeutic mAbs<sup>7</sup>.
- $C_{max}$  and  $AUC_{0-2\text{ wk}}$  values at the NOAEL dose in the 6-month SC cynomolgus monkey study exceed the clinical values at the maximum recommended human dose of 300 mg by 21-fold and 23-fold respectively.

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<sup>7</sup> Keizer, R. et al. (2010). Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clinical Pharmacokinetics*. 49, 493 – 507.

*Distribution*

- Mean steady state DX-2930 volume of distribution ( $V_d$ ) in cynomolgus monkeys following a single IV dose was approximately 0.15 L. This is approximately equivalent to the cynomolgus monkey total blood volume<sup>8</sup>. This is the expected  $V_d$  for a monoclonal antibody.
- The range of human DX-2930  $V_d$  values spanned from approximately 12 – 17 L at doses between 30 – 400 mg in study DX-2930-02. These values exceed the total blood volume in humans (approximately 5 L), suggesting that there is some distribution of DX-2930 beyond the blood volume and into the extracellular fluid.

*Metabolism*

- Metabolism studies were not conducted with DX-2930. The metabolic pathways of a therapeutic mAb are expected to be consistent with other endogenous antibodies (e.g. proteolysis in liver and phagocytic cells of the immune system).

*Elimination*

- DX-2930 clearance was reported to be 0.004 ml/min/kg in male and female monkeys. This value is consistent with published values for 13 other humanized IgG antibodies in cynomolgus monkeys<sup>9</sup>.
- DX-2930 clearance in humans ranged between 0.006 – 0.012 ml/min/kg, comparable to the values observed in monkeys. These values are generally consistent with clearance values reported for other approved therapeutic mAbs on a human IgG1 framework<sup>10</sup>.
- The mean  $T_{1/2}$  in cynomolgus monkeys after SC administration was between 9.5 – 11.5 days. Mean  $T_{1/2}$  was comparable in humans (14.0 days). These are consistent with expected  $T_{1/2}$  values for hIgG1 mAbs.
  - The long half-life is related to the binding of IgG to FcRn (protects against endosomal degradation) in endothelial cells

*Anti-drug antibodies*

- Neutralizing anti-drug antibodies (ADA) were present in all rats treated with SC DX-2930. For this reason, DX-2930 toxicity assessment was not possible in rats
- Anti-drug antibodies were detected at low incidence in cynomolgus monkeys and humans. These did not significantly affect DX-2930 exposure.

**Table 5. Summary of relevant pharmacokinetic parameters in humans, rats, and cynomolgus monkeys after repeated SC DX-2930 doses**

	Humans <sup>a</sup>	Rats (SD) <sup>b</sup>	Cynomolgus monkeys <sup>b</sup>	Cynomolgus monkeys <sup>b</sup>
Study	Applicant	(b) (4) 446031	(b) (4) 446033	(b) (4) 446051

<sup>8</sup> Ageyama, N. et al. (2001) Specific gravity of whole blood in cynomolgus monkeys, squirrel monkeys, and tamarins and total blood volume in cynomolgus monkeys. *Contemporary Topics in Laboratory Animal Science*. 40, 33 – 35.

<sup>9</sup> Deng, R. et al. (2011) Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: What have we learned? *mAbs*. 3, 61 – 66.

<sup>10</sup> Lobo et al. (2004) Antibody Pharmacokinetics and Pharmacodynamics. *Journal of Pharmaceutical Sciences*. 93, 2645 – 2668.

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	PK/PD analysis						
DX-2930 dose	300 mg (SC)	50 mg/kg (SC)		50 mg/kg (SC)		50 mg/kg (IV)	
Duration	Up to 6 months (1x every 2 weeks dosing)	4 weeks (1x weekly dosing)		6 months (1x weekly dosing)		4 weeks (1x weekly dosing)	
Sex	M & F	M	F	M	F	M	F
T <sub>max</sub>	3.7 days	2.0 days	0.8 days	3.2 days	2.5 days	0.6 hr	0.4 hr
C <sub>max</sub> (µg/ml)	35.0	61	7.4	741	747	1650	1630
T <sub>1/2</sub>	14.0 days	2.2 days	0.3 days	9.5 days <sup>c</sup>	11.5 days <sup>c</sup>	6.0 days	6.8 days
Volume of Distribution (L)	15.9	NR	NR	NR	NR	0.14	0.16
Clearance (ml/min/kg)	0.009	NR	NR	NR	NR	0.004	0.004
SC bioavailability	-	-	-	66% <sup>d</sup>	NR	-	-
AUC <sub>0-2 wks</sub> (µg*hr/ml)	9,550	5,890	201	222,000	220,000	127,000	119,000
ADA positive subjects	3.85% at d 182	6/6 Neutralizing	6/6 Neutralizing	1/6 Non-neutralizing	1/6 Non-neutralizing	1/5 Non-neutralizing	0/5 Non-neutralizing
<p><sup>a</sup> Population PK analysis <math>n = 27</math> for 300 mg SC group. The proposed clinical dose for DX-2930 is 300 mg Q2W.  <sup>b</sup> PK values are reported for NOAEL dose at the last time point of PK measurement  <sup>c</sup> Monkey SC T<sub>1/2</sub> values derived from single dose SC study (50 mg/kg) (b) (4) 446030. T<sub>1/2</sub> was not calculable in 6-month study due to insufficient data in the terminal phase of DX-2930 disposition.  <sup>d</sup> Monkey SC bioavailability data are derived from a single dose (20 mg/kg), non-GLP study in male cynomolgus monkeys only (Study (b) (4) 446027)  (NR = Not reported)</p>							

## 5.5. Toxicology

### 5.5.1. General Toxicology

**Study title/ number:** Study (b) (4) 446033: A 6-Month (Once weekly) subcutaneous injection toxicity study of DX-2930 in Cynomolgus monkeys

#### Key Study Findings

- No dose-limiting toxicities were identified. The target organs of toxicity were SC injection sites, although these findings were considered monitorable in a clinical setting.
- NOAEL = 50 mg/kg
  - Mean AUC<sub>0-168</sub> (M & F combined): 110,500 µg\*hr/ml
- A more detailed review of this study is found in the IND 116647 nonclinical review dated 3/12/15

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Conducting laboratory and location: (b) (4)  
GLP compliance: Yes

<b>Methods</b>	
<b>Dose and frequency of dosing:</b>	0, 5, 25, 50 mg/kg Once per week
<b>Route of administration:</b>	Subcutaneous (dorsal region)
<b>Dose volume:</b>	Control: 0.5 ml/kg 5 mg/kg: 0.05 ml/kg 25 mg/kg: 0.24 ml/kg 50 mg/kg: 0.48 ml/kg
<b>Formulation/Vehicle:</b>	(b) (4)
<b>Species/Strain:</b>	Cynomolgus monkey
<b>Number/Sex/Group:</b>	Main study: 4/sex/group Recovery: Control & HD: 2/sex/group
<b>Age:</b>	2.7 – 3.3 years
<b>Satellite groups/ unique design:</b>	No
<b>Deviation from study protocol affecting interpretation of results:</b>	No

**Observations and Results:**

<b>Parameters</b>	<b>Major findings</b>
<b>Mortality</b>	None
<b>Clinical Signs</b>	None
<b>Body Weights</b>	None
<b>Ophthalmoscopy</b>	None
<b>ECG</b>	None
<b>Hematology</b>	Females only: decreased total lymphocytes relative to controls at all doses (-5% to -32%) persisted from week 4 - 26
<b>Clinical Chemistry</b>	None
<b>Urinalysis</b>	*Moderate-abundant bacteria in 3/6 HD F *Appears to indicate increased incidence of potential urinary tract infection *Relationship to DX-2930 treatment is unclear
<b>Gross Pathology</b>	Dark red areas at injection site: 1/4 HD M; 2/4 HD F
<b>Organ Weights</b>	None
<b>Histopathology</b> <b>Adequate battery: Yes</b>	Injection site hemorrhage: 1/4 HD M; 2/4 HD F
<b>Toxicokinetics</b>	*No differences in DX-2930 exposure between males and females

	<p>*Systemic exposure increased proportionally with dose in both the first and last week of the study</p> <p>*DX-2930 accumulation ratios between week 25 &amp; week 1 were approximately 2.8 – 2.9 across all dose groups.</p> <p>*See Table 6 below</p>
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LD: low dose; MD: mid dose; HD: high dose.

-: indicates reduction in parameters compared to control.

**Table 6. Summary of toxicokinetic parameters after the first dose and during the final week of dosing in a 6-month study (1x weekly dosing) of DX-2930 in cynomolgus monkeys**

	Dose (mg/kg)	C <sub>max</sub> (µg/ml)			AUC <sub>0-168</sub> (µg*hr/ml)			Accum. ratio
		Male	Female	Mean	Male	Female	Mean	
Wk 1	5	25.0	30.9	28.0	3,180 ± 779	4,340 ± 515	3,760	
	25	118	166	142	15,000 ± 1,400	21,800 ± 4,300	18,400	
	50	266	344	305	34,100 ± 5,410	45,900 ± 3,140	40,000	
Wk 25	5	69.6 <sup>a</sup>	74.6	72.1	10,500 ± 1340	11,200 ± 1780	10,850	2.9
	25	327	394	360.5	49,100 ± 11,800	55,500 ± 3,210	52,300	2.8
	50	741	747	744	111,000 ± 24,900	110,000 ± 10,500	110,500	2.8

<sup>a</sup>LD male #6843 had no detectable plasma DX-2930 at week 25 due to neutralizing ADA.

### 5.5.2. Genetic Toxicology

Genetic toxicology studies are not applicable to mAbs and were not conducted with DX-2930.

### 5.5.3. Carcinogenicity

Shire submitted a written assessment of the carcinogenic potential of lanadelumab (DX-2930) in place of conducting rodent carcinogenicity studies. The conduct of a 2-year carcinogenicity study with DX-2930 in rodents was not feasible based on the evidence for development of neutralizing anti-drug antibodies in SD rats after repeated dosing for 4 weeks.

Shire's risk assessment was comprised of 4 main components: (1) reference to the results of repeated-dose toxicity studies in rats and monkeys with DX-2930; (2) carcinogenicity findings in other approved products that target the kallikrein-kinin system; (3) reference to expected cancer risk in humans with kallikrein deficiency, and (4) analysis of current scientific literature to assess the potential influence of chronic plasma kallikrein inhibition on tumor formation.

Additional analysis of the scientific literature as it relates to pKal knockout animals and the effects of bradykinin on tumor development is also included in the current review.

#### *Chronic toxicity studies*

There was no evidence for pre-neoplastic or neoplastic lesions in monkeys that received DX-2930 (SC) once weekly for 6 months at up to 50 mg/kg (Study (b) (4) 446033). The DX-2930 systemic exposure at this dose exceeds the predicted AUC at the maximum clinical dose of 300 mg by a factor of approximately 23-fold.

#### *Approved products that target the kallikrein-kinin system*

##### Kalbitor (Ecallantide)

Ecallantide (developed by Dyax and owned by Shire) was approved in the United States in 2009. This molecule is a 60-amino acid polypeptide (SC administration) indicated as an acute treatment for HAE attacks (up to 3 x 10 mg administrations per 24 hrs). Ecallantide inhibits plasma kallikrein function by blocking the binding site for its substrate, high molecular weight kininogen (HMWK).

Ecallantide was tested in a 2-year rat SC carcinogenicity study in which animals were dosed every 3 days. There was no evidence of tumor formation at doses up to 2-fold greater than the maximum recommended human dose on an AUC basis<sup>11</sup>. Furthermore, Shire reports that there has been no evidence for increased carcinogenicity risk in humans taking ecallantide.

#### *Carcinogenicity risk in prekallikrein deficient humans*

A total of 81 cases of humans with prekallikrein (precursor to plasma kallikrein) deficiency have been reported in the literature<sup>12</sup>. These patients lack functional plasma kallikrein. The most prominent feature of this condition is a greatly prolonged activated partial thromboplastin time (aPTT) relative to normal individuals. Prothrombin time (PT) and thrombin time (TT) are not affected. These patients are clinically normal and there is no evidence for increased bleeding or any other notable symptoms. Given the lack of notable symptoms of this condition, most cases of prekallikrein deficiency are likely undetected.

The main non-coagulation-related actions of plasma kallikrein are fibrinolysis, decreased blood pressure and increased vascular permeability. The authors report no significant effects on blood pressure or vascular permeability in patients with prekallikrein deficiency. Fibrinolytic activity has been reported as either normal or decreased in these patients. The overall prognosis for prekallikrein-deficient patients is reported to be similar to that for age-comparable normal subjects. The authors did not report an association between prekallikrein deficiency and increased risk of carcinogenicity.

#### *Plasma kallikrein knockout mouse model*

<sup>11</sup> KALBITOR drug product label. Dyax Corporation. Revised 3/2015.

<sup>12</sup> Girolami, A et al. (2010) Congenital prekallikrein deficiency. *Expert Review of Hematology*. 3, 685 – 695.

Prekallikrein, the precursor to plasma kallikrein, is encoded by the KLKB1 gene, located on chromosome 4q35<sup>13</sup>. Prekallikrein knockout mice (*Klkb1*<sup>-/-</sup>) have been generated by several research groups, and characterized in multiple publications. Bird et al.<sup>14</sup> evaluated these mice in the context of thrombus formation. Similar to prekallikrein deficient humans, prekallikrein knockout mice had increased aPTT without prolonged bleeding time. These mice were protected from occlusion after 3.5% FeCl<sub>3</sub>-induced arterial thrombosis. Stavrou et al.<sup>15</sup> also characterized prekallikrein knockout mice in the context of thrombosis protection. This study demonstrated that *Klkb1*<sup>-/-</sup> mice have plasma Bradykinin levels 29-fold lower than WT mice.

There are currently no published reports of lifetime studies of *Klkb1*<sup>-/-</sup> mice in which tumor formation has been evaluated. Such studies could provide insight related to the potential effects of chronic inhibition of pKal by DX-2930 in HAE patients.

#### *Role of bradykinin in tumor development*

The primary objective of pKal inhibition in the context of HAE is to disrupt bradykinin production. It is expected that chronic DX-2930 administration will result in a lowering of plasma bradykinin levels in humans that is comparable to that observed in *Klkb1*<sup>-/-</sup> mice. The potential influence that this might have on tumor formation is discussed below.

Bradykinin is a pleiotropic molecule that is considered to be pro-tumorigenic. Bradykinin, through its activation of the B2 and/or B1 receptors, has been shown to stimulate cell proliferation, cell migration and angiogenesis in multiple different experimental models.

In vitro studies have shown that bradykinin increases cell proliferation in multiple different cell types. Depending upon the cell type, kinins induce excitability, cell division, permeability, and stimulate the release of a variety of biologically active agents<sup>16</sup>.

Kinins, including bradykinin, can promote angiogenesis in different experimental models of normal and cancer cells/tissues, through activity at B1R, B2R or both<sup>17</sup>. Bradykinin has also been shown to enhance the migration of glioma and bladder cancer cells in vitro via B2R activation. This function, in addition to its vasoactive properties, suggests that bradykinin could contribute to tumor metastasis<sup>2</sup>.

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<sup>13</sup> Sotiropoulou G and Pampalakis G (2012) Targeting the kallikrein-related peptidases for drug development. *Trends in Pharmacological Sciences*. 33, 623 – 634.

<sup>14</sup> Bird, JE et al. (2012) Effects of plasma kallikrein deficiency on haemostasis and thrombosis in mice: Murine ortholog of the Fletcher Trait. *Thrombosis and Haemostasis*. 107, 1141-1150.

<sup>15</sup> Stavrou, E. et al. (2015) Reduced thrombosis in *Klkb1*<sup>-/-</sup> mice is mediated by increased Mas receptor, prostacyclin, Sirt1, and KLF4 and decreased tissue factor. *Blood*. 125, 710-719.

<sup>16</sup> Da Costa, P. et al. (2014) The role of kinin receptors in cancer and therapeutic opportunities. *Cancer Letters*. 345, 27 – 38.

<sup>17</sup> Yu HS, Wang SW, Chang AC, Tai HC, Yeh HI, Lin YM, et al. (2014). Bradykinin promotes vascular endothelial growth factor expression and increases angiogenesis in human prostate cancer cells. *Biochemical Pharmacology*; 87: 243-53

Bradykinin is produced as an autocrine factor to stimulate cell growth in some cancers, including small cell lung carcinoma (SCLC), prostate and breast cancer and certain ascites tumors<sup>16</sup>. Studies that examined B1R and B2R expression levels in clinical samples from cancer patients and cancer cell lines have suggested that B1R and/or B2R activity may contribute to malignant transformation and tumor progression. Disruption of the kallikrein-kinin system, specifically via antagonists for either B1R or B2R, has been proposed for the treatment of various cancers including lung, prostate and breast cancers<sup>18</sup>. Finally, *KLKB1* (prekallikrein gene) mRNA overexpression has been proposed as a putative molecular biomarker for chronic lymphocytic leukemia<sup>19</sup>.

Based on the available nonclinical data and published scientific literature, it can be concluded that inhibition of plasma kallikrein activity via DX-2930 treatment, resulting in reduced bradykinin production, is unlikely to affect malignancy risk in humans.

#### 5.5.4. Reproductive and Developmental Toxicology

##### Fertility and Early Embryonic Development

**Study title/ number:** Study P2930-13-02: 13-week repeat-dose fertility study of DX-2930 in sexually mature cynomolgus monkeys with a 4-week recovery

##### **Key Study Findings**

- LD and HD males had increased prothrombin time (~ +10% vs. control) at the end of the dosing period
  - The finding did not reverse in recovery period
  - Clinically monitorable finding: not considered dose limiting
- There were no DX-2930 related effects on male or female reproductive parameters
- NOAEL = 50 mg/kg
  - Mean AUC<sub>0-168</sub> (male & female) at NOAEL: 103,000 µg\*hr/ml
- A more detailed review of this study is found in the IND 116647 nonclinical review dated 3/12/15

<b>Conducting laboratory and location</b>	(b) (4)
<b>GLP compliance:</b>	Yes

<b>Methods</b>	
<b>Dose and frequency of dosing:</b>	0, 10, 50 mg/kg Once per week
<b>Route of administration:</b>	Subcutaneous

<sup>18</sup> Leeb-Lundberg, L. et al. (2005) International Union of Pharmacology. XLV. Classification of the kinin receptor family: from molecular mechanisms to pathophysiological consequences. *Pharmacological Reviews*. 57, 27 – 77.

<sup>19</sup> Adamopoulos, P. et al. (2015) KLKB1 mRNA overexpression: A novel molecular biomarker for the diagnosis of chronic lymphocytic leukemia. *Clinical Biochemistry*. 48, 849 – 854.

<b>Formulation/Vehicle:</b>	(b) (4)
<b>Species/Strain:</b>	Sexually mature male & female cynomolgus monkeys  Males: 5 – 6 years old Females: 3 – 8 years old (regularly cycling)
<b>Number/Sex/Group:</b>	Total: 5/sex/group Main study (13 weeks): 3/sex/group Recovery (+4 weeks): 2/sex/group  Animals were group housed (up to 3 animals/pen)
<b>Study design:</b>	<ul style="list-style-type: none"> <li>○ Assessment of <u>toxicity</u> was based on: <ul style="list-style-type: none"> <li>▪ Mortality</li> <li>▪ Clinical observations</li> <li>▪ Body weights</li> <li>▪ Clinical pathology</li> <li>▪ Anatomic pathology</li> </ul> </li> <li>○ Assessment of <u>male fertility</u> was based on: <ul style="list-style-type: none"> <li>▪ Testicular measurements</li> <li>▪ Semen analyses</li> <li>▪ Spermatogenesis staging</li> <li>▪ Reproductive organ evaluation</li> </ul> </li> <li>○ Assessment of <u>female fertility</u> was based on: <ul style="list-style-type: none"> <li>▪ Daily vaginal swabbing</li> <li>▪ Cycle length determination</li> <li>▪ Reproductive organ evaluation</li> </ul> </li> </ul>
<b>Deviation from study protocol affecting interpretation of results:</b>	No

### Observations and Results

Parameters	Major findings
<b>Mortality</b>	None
<b>Clinical Signs</b>	None
<b>Body Weights</b>	None
<b>Male reproductive parameters</b>	
<i>Testicular volume</i>	None
<i>Sperm motility, sperm count, sperm morphology</i>	None
<i>Spermatogenesis staging</i>	No abnormalities in normal progression of stages of spermatogenic cycle
<b>Female reproductive parameters</b>	
<i>Menstrual cycle length</i>	<ul style="list-style-type: none"> <li>▪ 2/5 HD females had prolonged cycle length</li> </ul>

	<ul style="list-style-type: none"> <li>▪ Relationship to DX-2930 treatment is equivocal based on evidence for comparable incidence of prolonged cycle length in control monkeys in published literature<sup>20</sup></li> </ul>
<b>Necropsy findings</b>	<ul style="list-style-type: none"> <li>▪ <u>Males</u>: There was no evidence for treatment related pathology to male sex organs including epididymis, testis, prostate, and seminal vesicle in any animals.</li> <li>▪ <u>Females</u>: <ul style="list-style-type: none"> <li>○ The ovaries of all main study females were considered mature.</li> <li>○ There were no treatment-related histopathology findings in any female sex organs examined microscopically including cervix, ovary, uterus, and vagina.</li> </ul> </li> </ul>

Prenatal and Postnatal Development

**Study title/ number:**

Study P8026M-SHP643: Enhanced Pre- and Postnatal Developmental Toxicity Study with DX-2930 in Cynomolgus Monkeys

**Key Study Findings**

- DX-2930 had no effect on maintenance of pregnancy or infant delivery
- There was no evidence for DX-2930 treatment mediated maternal toxicity
- DX-2930 was detected in infant plasma out to LD 90
  - DX-2930 concentration in infant plasma was approximately ½ the concentration in maternal animals
- DX-2930 was detected in maternal milk at approximately 0.2% of the maternal plasma concentration.
- There was no evidence for effects of maternal DX-2930 treatment on any behavioral, physical, or neurological measurements in F1 offspring
- NOAEL doses:
  - Maternal NOAEL: 50 mg/kg
  - Fetal/infant NOAEL: 50 mg/kg

<b>Conducting laboratory and location:</b>	(b) (4)
<b>GLP compliance:</b>	Yes

<b>Methods</b>	
<b>Dose and frequency of dosing:</b>	Group 1: 0 (vehicle) Group 2: 10 mg/kg Group 3: 50 mg/kg  Dose frequency: Once per week

<sup>20</sup> Bussiere, J. et al. (2013) Assessment of menstrual cycle length in cynomolgus monkeys as a female fertility endpoint of a biopharmaceutical in a 6 month toxicity study. *Regulatory Toxicology and Pharmacology*. 66, 269 – 278.

<b>Route of administration:</b>	Subcutaneous injection
<b>Formulation/Vehicle:</b>	(b) (4)
<b>Species/Strain:</b>	Cynomolgus monkey
<b>Number/Sex/Group:</b>	18 naïve females/group
<b>Study design:</b>	<ul style="list-style-type: none"> <li>▪ Sexually mature males were used for mating only</li> <li>▪ Females were paired with males for a maximum of 48 hours during the time of expected ovulation</li> <li>▪ Ultrasonic examinations were done at 18, 19, and 20 days post-coitum to confirm pregnancy</li> <li>▪ DOSING PERIOD: Once per week from Gestation Day (GD) 20 – delivery (approximately GD 162)</li> <li>▪ Note that this dosing period is consistent with the guidelines for ePPND studies in the ICH S6 Addendum</li> <li>▪ Pregnancy was monitored by ultrasonography (to assess vitality) on GD 27, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160 and at subsequent 3-day intervals until delivery</li> <li>▪ Maternal animals and F1 offspring were retained on study until postnatal day 92</li> </ul>
<b>Deviation from study protocol affecting interpretation of results:</b>	No

## Observations and Results

### F<sub>0</sub> Dams

#### *Survival*

Premature deaths in maternal animals were observed in all study groups (Table 7). There was no apparent relationship of premature deaths to DX-2930 treatment.

**Table 7. Summary of premature deaths of maternal animals in monkey EFD study with DX-2930**

<b>Dose</b>	<b>Animal #</b>	<b>Day of death</b>	<b>Description</b>
Vehicle	130994	GD 139	<ul style="list-style-type: none"> <li>• Moribund sacrifice: Birth difficulties</li> <li>• No remarkable gross observations at necropsy</li> </ul>
	140714	GD 169	<ul style="list-style-type: none"> <li>• Moribund sacrifice: Birth difficulties</li> <li>• No remarkable gross observations at necropsy</li> </ul>
	151334	Social day 38	Sacrificed due to aggressive behavior
10 mg/kg	130460	GD 160	<ul style="list-style-type: none"> <li>• Moribund sacrifice: Birth difficulties</li> <li>• Liver: discolored (tan)</li> <li>• Adrenal: discolored (red)</li> <li>• Skin: Alopecia, multiple regions over 10 mm<sup>2</sup> in abdomen</li> </ul>

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Dose	Animal #	Day of death	Description
			<ul style="list-style-type: none"><li>• DX-2930 plasma conc: 112,000 ng/ml at LD 0</li></ul>
50 mg/kg	142210	GD114	<ul style="list-style-type: none"><li>• Moribund sacrifice: abortion complications</li><li>• No remarkable gross observations at necropsy</li></ul>
	144112	LD 3	<ul style="list-style-type: none"><li>• Moribund sacrifice after Infant failure to thrive</li><li>• No remarkable gross observations at necropsy</li><li>• DX-2930 plasma conc: 574,000 ng/ml at LD 0</li></ul>

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*Pregnancy outcome*

Abortions were confirmed by negative ultrasonography. Stillbirths were confirmed based on a negative lung flotation test. The first trimester was defined as GD 21 – 50, the second trimester was defined as GD 51 – 100, and the third trimester was defined as after GD 101.

Results

There was no evidence for an effect of DX-2930 on pregnancy outcome. The mean gestation length ranged between 160 – 163 days across all groups (Table 8). Fetal loss occurred to a comparable extent in controls and DX-2930 treated animals. The majority of losses occurred during the first trimester. These losses are unlikely to be related to DX-2930 as fetal exposure to mAbs is expected to be low during the first trimester in both non-human primates and humans.

There were also 2 postnatal deaths in each group, all occurring in the first week after birth. These fetal loss values are all consistent with published data of vehicle-treated cynomolgus monkeys in 14 different PPND studies conducted between 1981-2007<sup>21</sup> (from laboratories at (b) (4) and (b) (4)).

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<sup>21</sup> Jarvis, P. et al. (2010) The cynomolgus monkey as a model for developmental toxicity studies: Variability of pregnancy losses, statistical power estimates, and group size considerations. *Birth Defects Research (Part B)*. 89, 175-187.

**Table 8. Summary of pregnancy outcome data in ePPND study conducted with SC DX-2930 in pregnant cynomolgus monkeys**

Dose (mg/kg)	Pregnant females	Mean Gestation Length (days)	Fetal/Infant Loss						
			1 <sup>st</sup> trimester (GD 21 - 50)	2 <sup>nd</sup> trimester (GD 51 – 100)	3 <sup>rd</sup> trimester (>GD 101)	Stillbirths	Total abortions & stillbirths	Postnatal death of offspring	Total surviving offspring
0	18	160	2 (11%)	1 (6%)	0 (0%)	2 (11%)	5 (28%)	2	11
10	18	163	2 (11%)	0 (0%)	0 (0%)	1 (6%)	3 (17%)	2	13
50	18	162	2 (11%)	0 (0%)	1 (6%)	1 (6%)	4 (22%)	2	12

Additional details related to the observed fetal/infant losses are discussed under F1 Generation: Survival.

#### *Necropsy observations*

All surviving maternal animals were sacrificed on LD 92. Macroscopic examination was conducted on all animals.

There were no remarkable findings upon macroscopic examination of any animals at the conclusion of the study.

#### *Toxicokinetics*

##### Blood

Blood samples were collected from all maternal animals for quantitation of DX-2930 exposure on GD 20, 90 and 146 at the following time points: pre-dose, 1, 8, 24, 48, 96, 168 hrs post dose. Blood samples were also collected at a single time point from maternal animals and infants on LD 7, 21, and 90 for DX-2930 quantitation.

DX-2930 exposure increased approximately proportionally with dose. Accumulation was observed between GD 20 and GD 90, but AUC values were comparable between GD 90 and GD 146. The data suggests that steady state was achieved at a time point between GD 20 and GD 90. Although anti-drug antibodies (ADA) were detected in the plasma of a subset of animals (see below), there was a minimal overall effect of ADA on DX-2930 exposure in this study.

**Table 9. Summary of mean C<sub>max</sub> and AUC<sub>0-168</sub> data in maternal monkey plasma in ePPND study with DX-2930**

Gestation day	10 mg/kg			50 mg/kg		
	C <sub>max</sub> (µg/ml)	T <sub>max</sub> (h)	AUC <sub>0-168</sub> (µg*hr/ml)	C <sub>max</sub> (µg/ml)	T <sub>max</sub> (h)	AUC <sub>0-168</sub> (µg*hr/ml)

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GD 20	81.3	94.7	11300	451	82.7	61000
GD 90	210	48.5	30600	1090	54.0	159000
GD 146	192	39.4	28100	1110	55.4	159000

Milk

Milk samples were collected on LD 7 and 28. A 0.1 ml intramuscular injection of oxytocin (2 U/dose) was administered prior to the start of milk collection.

DX-2930 was detected in maternal milk at LD 7, but at concentrations approximately 500-fold lower than the concentration detected in the plasma (Table 10). DX-2930 was still detectable in maternal milk at LD 28.

**Table 10. Mean DX-2930 values in plasma and milk of female monkeys during the lactation period**

Maternal DX-2930 dose	10 mg/kg			50 mg/kg		
	Plasma (ng/ml)	Milk (ng/ml)	Plasma: milk ratio	Plasma (ng/ml)	Milk (ng/ml)	Plasma: milk ratio
LD 7	109000	192	568	425000	931	456
LD 28	NR	42.6	NR	NR	320	NR

Pregnant monkeys were administered DX-2930 from GD20 until parturition. NR: not reported

Anti-drug antibodies

- Anti-drug antibodies (ADA) were detected in maternal monkeys in vehicle and DX-2930 treated monkeys (Table 11).
  - ADA detected in the vehicle group were at very low titers and likely represent nonspecific findings associated with the assay.
  - ADA resulted in elimination of DX-2930 exposure in a single animal in the LD group (# 142208).
  - ADA detected in other animals did not have a notable effect on DX-2930 exposure (based on comparison to other animals in their respective dose groups).
  - Taken together, it can be concluded that ADA had a very limited impact on DX-2930 exposure in maternal animals in this study.

**Table 11. Incidence of ADA formation in plasma of maternal animals in ePPND study**

Study Day	Vehicle	10 mg/kg	50 mg/kg
GD 20 (prior to first DX-2930 dose)	0/20	1/19 144100 (10)	0/18
GD 90	0/15	3/16 130460 (4434) 142208 (32500) <sup>a</sup>	4/16 140695 (73) 144122 (463)

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		151335 (1510)	153461 (145) 153463 (10200)
GD 146	1/14 151328 (77)	2/16 142208 (575000) <sup>a</sup> 151335 (591)	1/15 153463 (18700)
LD 7	2/12 151328 (141) 153485 (105)	2/13 142208 (515000) <sup>a</sup> 151335 (631)	1/13 153463 (9570)
LD 21	1/11 151328 (190)	2/13 142208 (421000) <sup>a</sup> 151335 (378)	1/12 153463 (2900)
LD 90	0/11	2/13 142208 (34400) <sup>a</sup> 151335 (453)	5/12 153463 (555) 153122 (33) 144108 (64) 144122 (158) 160082 (23)
<sup>a</sup> ADA resulted in elimination of DX-2930 exposure in this animal Specific animal numbers are listed below the incidence values. Titer values are listed in parentheses.			

F<sub>1</sub> Generation

*Survival*

Each treatment group was comprised of at least 11 infants at PND 7. This exceeds the minimum recommended value of at least 6 – 8/group in the ICH S6 Addendum.

**Table 12. Total # of F1 animals per treatment group in DX-2930 ePPND study**

Maternal DX-2930 dose (mg/kg)	# of dams	Total surviving offspring at PND 7
0	18	11
10	18	13
50	18	12

- Details regarding infant loss are included in Table 13. For those infants lost due to abortion, there were no notable clinical observations, clinical chemistry changes, or body weight changes in the respective maternal animals. There was no evidence for an effect of DX-2930 on the incidence of stillbirths or on infant deaths during the early postnatal period.
- 2 infants in each study group died within the first 7 days of birth. There was no evidence for a relationship between DX-2930 treatment and incidence of infant mortality.
- The Applicant notes that the incidence of infant deaths was within an expected range based on the published literature<sup>21</sup>. The hearts of these animals, examined at necropsy, were all considered to be within normal limits for infants at or near the day of parturition.

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**Table 13. Description of fetal and infant losses observed in ePPND study with SC DX-2930 in pregnant cynomolgus monkeys**

Dose (mg/kg)	Sex	Animal #	Day of death	Cause of death	Description
0	ND	151334 (maternal)	GD 24	Abortion	Maternal severe vaginal bleeding on GD 24
	ND	142209 (maternal)	GD 34	Abortion	No heartbeat on ultrasound. No notable findings with maternal animal
	ND	130441 (maternal)	GD 62	Abortion	No heartbeat on ultrasound. No notable findings with maternal animal
	M	130994-1 (infant)	GD 139	Birth difficulties, stillborn	Discolored inguinal skin in maternal animal starting at GD 76
	M	140714-1 (infant)	GD 169	Birth difficulties, stillborn	Fetus was present in breach position
	F	160088-1 (infant)	PND 0	Moribund sacrifice, trauma	<u>Skin/subcutis</u> *erosion/ulcer: moderate *hemorrhage, slight *Exudate, slight
	F	144098-1 (infant)	PND 7	Found dead	*Low birth weight (252 g; ~30% less than other 2 control infant females) *Thorax circumference: 1.5 cm *Hypoactive, pale
10	ND	144106 (maternal)	GD 27	Abortion	Negative ultrasound. No remarkable observations
	ND	160085 (maternal)	GD 27	Abortion	No remarkable observations
	M	130460-2 (infant)	GD 160	Birth difficulties, stillborn	No remarkable observations
	M	153466-1 (infant)	PND 0	Found dead	Cause not determined. No remarkable findings upon macroscopic or microscopic examination
	F	160112-1 (infant)	PND 2	Found dead	Cause not determined *Low birth weight (297 g; ~10% less than other females in group) *Lung; inflammation, mixed cell; slight
50	ND	160121 (maternal)	GD 27	Abortion	Skin & pelage, midline abdomen, discolored (red), GD 20

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Dose (mg/kg)	Sex	Animal #	Day of death	Cause of death	Description
	ND	153478 (maternal)	GD 39	Abortion	No heartbeat on ultrasound. No notable findings with maternal animal
	ND	142210 (maternal)	GD 114	Abortion. Fetus delivered at GD 114.	No remarkable observations
	M	130995-1 (infant)	GD 148	Birth difficulties, stillborn	Found dead, cannibalized
	F	144112-1 (infant)	PND 3	Failure to thrive	*Dehydrated, jaundiced, and hypothermic on LD 3. Infant did not respond to veterinary intervention and was euthanized *Lung: discolored, all lobes, red/dark red, up to 2 mm <sup>2</sup> *Lung: congestion
	F	144095-1 (infant)	PND 7	Moribund sacrifice, head trauma	*Brain: hemorrhage; marked (red blood cells present within cerebral cortex, meninges, ventricles) *Skin/subcutis: hemorrhage, minimal
Maternal animal numbers are listed for abortions. Infant numbers are listed for stillbirths and postnatal deaths. Infant losses during the early postnatal period are noted by gray highlight. ND: Not determined					

***F1 Body weight***

Body weights were measured once weekly beginning on PND 1 and continuing to necropsy on PND 92.

***Birth weight***

Mean birth weight of HD male offspring was slightly decreased (-11%) relative to males born to vehicle-treated mothers (Table 14). There was no such effect observed in female monkeys. The relationship of this apparent effect to DX-2930 treatment is equivocal for the following reasons:

- There is a high degree of variability in birth weight values as evidenced by the large standard deviation values
- There is no effect on birth weight in female offspring

**Table 14. Mean birth weight data in F1 offspring of maternal animals treated with once weekly SC DX-2930 in ePPND study in monkeys**

Maternal DX-2930 (mg/kg)	F <sub>1</sub> Males			F <sub>1</sub> Females		
	0	10	50	0	10	50
<b>PND 1</b>						
<i>n</i>	8	4	6	3	10	8
Mean body weight (g)	376 ± 70	355 ± 16	333 ± 50	315 ± 59	326 ± 38	312 ± 46
% vehicle	100%	94%	89%	100%	103%	99%

### Body weight

Body weight gains in infants over the 3-month observation period showed no apparent relationship to DX-2930 treatment.

### F1 Toxicokinetics

Blood samples were collected from maternal and F1 animals at a single time point on LD 7, 21, and 90. DX-2930 was quantified using a validated capture assay as described for F0 animals above.

### Results

- F1 monkeys were exposed to DX-2930 indicating that DX-2930 could cross the placenta.
  - Mean plasma DX-2930 concentration was approximately 2-fold higher in maternal animals relative to their offspring on LDs 7 and 21.
  - DX-2930 was still detectable in the plasma of mothers and infants at LD 90 at approximately equal concentrations (Table 15).

**Table 15. Summary of mean DX-2930 plasma concentrations in maternal animals and infants at time points during the lactation period**

Maternal DX-2930 dose	10 mg/kg			50 mg/kg		
	Maternal (ng/ml)	Infant (ng/ml)	Maternal: infant ratio	Maternal (ng/ml)	Infant (ng/ml)	Maternal: infant ratio
LD 7	109000	52800	2.4	425000	268000	1.8
LD 21	42400	29100	1.7	219000	140000	1.7
LD 90	1110	1480	0.96	7230	5800	1.2

Note that the mean maternal: infant ratio values represent the mean of all individual parent: infant values (and not the overall mean maternal: mean infant values)

*F1 Anti-drug antibodies*

- ADA were detected in the plasma of the offspring of the 2 LD and 1 HD maternal animals that had the highest ADA titers (Table 16). There was no detectable DX-2930 in plasma of #142208-1, consistent with the evidence in its mother. The presence of ADA in LD animal 151335-1 and HD animal 153463-1 resulted in slightly lower DX-2930 plasma concentration compared to other animals in their respective dose groups.
- The totality of the data shows that ADA had limited impact on DX-2930 exposure in F1 offspring.

**Table 16. Incidence of ADA formation in plasma of F1 offspring of maternal animals that received SC DX-2930 from GD20 until parturition**

Study Day	Vehicle	10	50
PND 7	2/11 113332-1 (40) 151328-1 (22) <sup>a</sup>	2/13 142208-1 (178000) <sup>a</sup> 151335-1 (123) <sup>a</sup>	1/13 153463-1 (1350) <sup>a</sup>
PND 21	1/10 151328-1 (19) <sup>a</sup>	2/13 142208-1 (NR) <sup>a</sup> 151335-1 (36) <sup>a</sup>	1/12 153463-1 (11800) <sup>a</sup>
PND 90	0/11	1/12 142208-1 (11900) <sup>a</sup>	1/12 153463-1 (32) <sup>a</sup>

<sup>a</sup> Indicates that ADA were detected in the plasma of the respective maternal animal  
Specific animal numbers are listed below the incidence values. Titer values are listed in parentheses.

*F1 Physical development*

External examinations

- External examinations were recorded on PND 1, 7, 14, 21, 28 and every 4 weeks thereafter to PND 91.
- There was no evidence for effects of maternal DX-2930 treatment on the external features of male or female monkeys.

Morphological examinations

- Standard morphological measurements were recorded from each animal on PND 1, 21, 56, and 91.
- There was no evidence for effects of maternal DX-2930 treatment in any animals at any time point

Grip Strength

- Grip strength was measured on PND 28. Animals were tested for their ability to hang on a bar for a minimum of 30 seconds.
- There was no evidence for effects of maternal DX-2930 treatment in any animals at any time point

Assessment of skeletal development

- The developmental stage of bones in each infant was assessed via X-ray by an external consultant under non-GLP conditions on PND 35 (±2 days)

- There was no effect of maternal DX-2930 treatment on radius: tibia length in F1 offspring.
- No overt skeletal abnormalities were observed in any animal.

#### *F1 Neurological assessment*

##### Neurobehavioral test battery

- Neurological examinations were conducted on infants on PND 1 and 7 in a 3-part neurobehavioral test battery consistent with the endpoints outlined by Weinbauer et al.<sup>22</sup>.
- There was no evidence for effects of maternal DX-2930 treatment on any of the parameters evaluated in Parts 1, 2, or 3 of the test battery in infants on PND 1 or 7.

#### *F1 Necropsy Observations*

- All surviving F1 animals were sacrificed on PND 92. A macroscopic examination of the external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues was performed. Organ weights were recorded for all major organs. A complete battery of tissues was examined microscopically in all infants.
- There were no notable maternal DX-2930-related effects on macroscopic or microscopic findings in F1 animals.
- There were no effects of maternal DX-2930 treatment on mean organ weight in F1 animals.

## **5.6 Exposure margins**

#### *Human DX-2930 systemic exposure*

The maximum recommended human dose (MRHD) of DX-2930 is 300 mg q2w. The Applicant's predicted steady-state AUC<sub>2 weeks</sub> for this dose is 9550 µg\*hr/ml. This value is based on a Population PK analysis using data from clinical studies DX-2930-01, DX-2930-02, and DX-2930-03.

#### *General toxicology*

Study (b) (4) 446033, a 39-week SC study in cynomolgus monkeys (once weekly dosing) was the pivotal toxicology study to support marketing approval of DX-2930. No dose-limiting toxicities were identified. The mean AUC<sub>0-168</sub> at the no observed adverse effect level (NOAEL) of 50 mg/kg was 110,500 µg\*hr/ml. Once weekly dosing was used in this study, while clinical DX-2930 dosing is once every 2 weeks. The mean AUC<sub>last</sub> values for males and females from Study (b) (4) 446033 were doubled to allow for appropriate AUC comparison with the reported clinical AUC value from the 300 mg q2w dose regimen. The AUC<sub>2 weeks</sub> at the monkey NOAEL is approximately 23-fold higher than the clinical AUC at the MRHD.

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<sup>22</sup> Weinbauer G. et al. (2013) The enhanced pre- and postnatal development study for monoclonal antibodies. *Methods in Molecular Biology*. 947, 185 – 200.

*Reproductive toxicity*

Fertility

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. The NOAEL in this study was identified at 50 mg/kg. This dose is associated with a mean AUC<sub>2weeks</sub> of 210,000 µg\*hr/ml and 202,000 µg\*hr/ml in males and females respectively. These values are 22-fold and 21-fold higher than the clinical AUC at the MRHD

Enhanced pre- and postnatal development

In an enhanced pre- and post-natal development study, pregnant female cynomolgus monkeys were treated with 10 mg/kg or 50 mg/kg DX-2930 (SC) from GD 20 – delivery (approximately GD 163). Maternal animals and their offspring were monitored out to PND 92.

There was no evidence for DX-2930-mediated maternal toxicity, nor were there any observed effects on maintenance of pregnancy or infant delivery. Furthermore, there were no observed effects of maternal DX-2930 treatment on physical development or on behavioral and neurological measurements in F1 offspring.

DX-2930 was detected in maternal milk at approximately 0.2% of the maternal plasma concentration. DX-2930 was measured in infant plasma at approximately ½ the concentration in maternal animals out to LD 21. DX-2930 crossed the placenta in monkeys. DX-2930 was still detectable in maternal and infant plasma at LD 90 (approximately equivalent concentrations).

The maternal NOAEL and the fetal/developmental NOAEL in this study were both defined at 50 mg/kg. This dose was associated with a maternal AUC<sub>2 weeks</sub> of 318,000 µg\*hr/ml at GD 146. This value is 33-fold higher than the clinical AUC at the MRHD (Table 17).

**Table 17. Summary table showing DX-2930 systemic exposure values at NOAEL doses in relevant toxicity studies in comparison to the human steady state DX-2930 systemic exposure at the MRHD of 300 mg every 2 weeks**

Human		Monkey					
Population PK			General Tox		Fertility		ePPND
MRHD	300 mg q2w	NOAEL	50 mg/kg		50 mg/kg		50 mg/kg <sup>b</sup>
AUC <sub>0-2 wks</sub> (µg*hr/ml)	9550 <sup>a</sup>	AUC <sub>0-2 wks</sub> (µg*hr/ml)	M	F	M	F	F
			220,000	222,000	210,000	202,000	318,000
		Exposure margin	23	23	22	21	33

<sup>a</sup>AUC<sub>2 wks</sub> based on population PK analysis of all subjects (n = 27) treated with DX-2930 at 300 mg q2w (Applicant's Population PK/PD analysis, clinical studies DX-2930-01; DX-2930-02; DX-2930-03)

<sup>b</sup> 50 mg/kg NOAEL value in ePPND study applies to both the maternal NOAEL and the fetal/infant NOAEL

## 5.7 Labeling

### *Suggested revisions to the nonclinical portions of the labeling*

Revisions to the Applicant's proposed language for the nonclinical sections of the labeling are provided below. Underlined text is to be inserted while ~~strike through~~ text is to be deleted from the TAKHZYRO label.

-----INDICATIONS AND USAGE-----

<TRADENAME> TAKHZYRO is a plasma kallikrein inhibitor (monoclonal antibody) (b) (4) indicated for prophylaxis to prevent attacks (b) (4) of hereditary angioedema (HAE) in patients 12 years and older. (1)

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

(b) (4)

There are no available data on TAKHZYRO use in pregnant women to inform any drug associated risks. Monoclonal antibodies such as lanadelumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. An enhanced pre-and postnatal development (ePPND) study conducted in pregnant monkeys at doses up to 33 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the developing fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### Data

##### *Animal Data*

(b) (4)

In the ePPND study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of lanadelumab at doses up to 33 times the MRHD (on an AUC basis with maternal subcutaneous doses up to 50 mg/kg/week) from gestation day 20 at the beginning of organogenesis through to parturition. There were no lanadelumab- related effects on maintenance of pregnancy or parturition. Maternal lanadelumab treatment had

(b) (4)

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no effects on embryo-fetal development, survival, growth, or postnatal development of offspring through 3 months of age. Lanadelumab crossed the placenta in monkeys. Offspring were exposed to lanadelumab at approximately 50% of the maternal plasma concentration out to postnatal day 21 (PND 21). Lanadelumab concentrations were approximately equivalent in maternal and offspring plasma at PND 90.

8.2 Lactation

Risk Summary

(b) (4)  
There are no data on the presence of lanadelumab in human milk (b) (4)  
(b) (4) its effects on the breastfed infant, or its effects on milk production. Lanadelumab was detected in the milk of lactating cynomolgus monkeys at approximately 0.2% of the plasma concentration. The developmental and health benefits of breastfeeding should be (b) (4) considered along with the mother's (b) (4) clinical need for TAKHZYRO and (b) (4) any potential adverse effects on (b) (4) the breastfed infant from TAKHZYRO or from (b) (4) underlying maternal condition.

Data

*Animal Data*

Available pharmacokinetic data in cynomolgus monkeys have shown excretion of lanadelumab in milk at approximately 0.2% of the maternal plasma (b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lanadelumab is a fully human monoclonal antibody (IgG1/ κ-light chain) (b) (4)  
(b) (4) that binds plasma kallikrein and inhibits its (b) (4)  
proteolytic activity. (b) (4)  
Plasma kallikrein (b) (4) is a protease (b) (4)  
that cleaves high-molecular-weight-kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin, a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. (b) (4)  
(b) (4) In patients with HAE due to C1-inhibitor (C1-INH) deficiency or dysfunction, (b) (4)  
(b) (4) normal regulation of plasma kallikrein activity, (b) (4)  
(b) (4) -is not present. Increased plasma kallikrein activity leads to angioedema attacks.  
Lanadelumab (b) (4) limits bradykinin generation in patients with HAE.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

<sup>25</sup> Module 2.7.4 Summary of Clinical Safety Sec 5.4

<sup>26</sup> Module 2.6.6 Toxicology Written Summary, Section 6.3

(b) (4)

Animal studies have not been conducted to evaluate the carcinogenic potential of lanadelumab. Published literature supports bradykinin, which is elevated in HAE, as a pro-tumorigenic molecule. However, the malignancy risk in humans from an antibody that inhibits plasma kallikrein activity, such as lanadelumab, is currently unknown.

Male and female fertility were unaffected based upon no observed adverse histopathological findings in the reproductive organs from sexually mature cynomolgus monkeys that received lanadelumab for 13 weeks at subcutaneous doses up to 50 mg/kg/week (approximately 22 times the MRHD on an AUC basis).

X Matthew Whittaker

Primary Reviewer

X Timothy Robison

Team Leader

X Tim McGovern

Associate Director, ODE, OND Immediate Office

(e-signatures located on the last page)

## 6 Clinical Pharmacology

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### 6.1. Executive Summary

BLA 761090 consists of two Phase 1 studies that were conducted in healthy adults (Study DX-2930-01) or adults with HAE (Study DX-2930-02). Two Phase 3 studies were conducted in subjects aged 12 years and older with HAE, including a double-blind, placebo-controlled Phase 3 study (DX2930-03), and an open-label Phase 3 extension study (DX2930-04):

Clinical Pharmacology properties of lanadelumab support the following proposed dosing regimen in patients with HAE aged 12 years and older:

*The recommended starting dose is 300 mg every 2 weeks. A dosing interval of 300 mg every 4 weeks is also effective and may be considered in those patients well-controlled after (b) (4) 6 months*

The following are the major clinical pharmacology findings of the current review:

1. The dosing regimen of lanadelumab has been adequately explored. Pivotal trial DX-2930-03 evaluated three dosing regimens (300 mg Q2W, 300 mg Q4W, and 150 mg Q4W), all of which were effective compared to placebo. However, there was no clear dose response in this study. Numerically, the magnitude of the treatment effect (monthly attack rate, time to first attack, attack-free rate) was the largest in the lanadelumab 300 mg Q2W treatment arm, while interestingly, the lowest dose of 150 mg Q4W had numerically better efficacy compared to 300 mg Q4W.

The apparent lack of dose response can partially be explained by the limited sample size and number of patients with high attack frequency in the 300 mg Q4W treatment group. In the OLE study DX2930-04 where all patients were given the same dosing regimen of 300 mg Q2W, it appears as if more “non-responders” (patients who continue to have multiple attacks while on lanadelumab) were initially assigned to the 300 mg Q4W arm (See section 6.3.2 for details). This imbalance may explain why the efficacy in the 300 mg Q4W arm appeared to be numerically worse than the efficacy in the 150 mg Q4W in study DX2930-03.

2. In Study DX2930-03, lanadelumab 300 mg Q2W demonstrated better efficacy (numerically) than 150 mg Q4W. Confirmation of these results can be found in the OLE where 150 mg Q4W rollover subjects showed a statistically significant decrease in attack rate, as well as improvement in time to first attack, and higher attack free rate after transitioning to 300 mg Q2W (See section 6.3.2 for details).

3. While lanadelumab 300 mg Q2W also demonstrated better efficacy (numerically) than 300 mg Q4W in study DX2930-03, we note that the 300 mg Q4W rollover subjects did not have a significant decrease in attack rate after transitioning to 300 mg Q2W in the OLE. Though dose escalation from Q4W to Q2W led to slightly better efficacy at the beginning of the OLE, after the first 4 months, efficacy outcomes were similar between study DX2930-03 and the OLE in this group of patients regardless of the dosing regimen.
4. An exposure response analysis for efficacy was performed using data in Study DX-2930-03. The exposure response is consistent with the observed data in rollover patients in Study DX2930-03 and DX2030-04: the efficacy is similar for 300 mg Q4W and 300 mg Q2W after 4 months. No further improvement in efficacy is expected after dosing for 6 months.
5. There is no clear dose/exposure-response relationship for safety endpoints. The safety profile of all doses assessed in phase 3 studies is considered acceptable (See section 8.2).
6. Following subcutaneous administration, the pharmacokinetics of lanadelumab was approximately dose proportional in the therapeutic dose range in patients with HAE. Following subcutaneous administration of lanadelumab, peak plasma concentrations are reached within 5 days, and terminal elimination half-life is ~2 weeks. The anticipated population time to reach steady state concentration was approximately 70 days. At steady-state, the mean accumulation ratio is approximately 1.44, 1.42, and 2.43 for dosing regimen of 150 mg Q4W, 300 mg Q4W and 300 mg Q2W, respectively.
7. No effect of body site injection (upper arm, thigh or abdomen) on PK of lanadelumab was observed. Similar exposure of lanadelumab was observed following SC administration by either health care provider or self-administration. The use of analgesics, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic had no effect on PK of lanadelumab.
8. Concentration-dependent inhibition of plasma kallikrein, measured as reduction of cHMWK levels, was demonstrated after SC administration of lanadelumab 150 mg Q4W, 300 mg Q4W or 300 mg Q2W in subjects with HAE. The PK-PD relationship between lanadelumab and cHMWK is described by an indirect exposure-response pharmacological model with a maximum 53.7% inhibition of formation rate of cHMWK. The estimated time for cHMWK values to return to within 5% of baseline following the last dose for the 150 mg q4wk, 300 mg q4wk and 300 mg q2wk regimens were approximately 139, 154 and 163 days, respectively, suggesting the inhibition of cHMWK was reversible
9. No adjustment of the starting dose is recommended for any intrinsic or extrinsic factors.

10. There was no difference in lanadelumab exposure or cHMWK levels between HAE subjects positive or negative for antidrug antibodies (ADA) or antibodies classified as neutralizing, suggesting formation of ADA or neutralizing antibodies has no effect on either PK or PD in addition to the prevention of HAE attacks

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

#### Pharmacokinetics in HAE Patients

Following subcutaneous administration, the pharmacokinetics of lanadelumab-flyo was approximately dose proportional in the therapeutic dose range in patients with HAE. Following subcutaneous administration of TAKHZYRO, peak plasma concentrations are reached within 5 days, and terminal elimination half-life is ~2 weeks (See section 6.3.1 for details). The anticipated population time to reach steady state concentration was approximately 70 days. At steady-state, the mean accumulation ratio is approximately 1.44, 1.42, and 2.43 for dosing regimen of 150 mg Q4W, 300 mg Q4W and 300 mg Q2W, respectively.

#### Pharmacokinetics in Special Populations

The main source of intrinsic PK variability identified in patients using population PK analysis is body weight, with a decrease in weight resulting in an increase in exposure, however no dose adjustment is needed (see section 6.3.1). None of the other demographic characteristics (age, race, or sex) have a relevant effect on the PK of lanadelumab after correcting for body weight.

No formal study was conducted in special populations (such as patients with renal or hepatic impairment), because the disposition of lanadelumab, an IgG antibody, is not expected to be impacted by renal or hepatic function.

In pediatric patients, the mean lanadelumab-flyo ( $\pm$ SD) AUC<sub>ss</sub> was 629 (204)  $\mu\text{g}\cdot\text{day}/\text{mL}$  following SC administration of TAKHZYRO 300 mg Q2W in pediatric patients 12 to less than 18 years of age. This is approximately 37% higher than the mean AUC<sub>ss</sub> in adult patients (460  $\mu\text{g}\cdot\text{day}/\text{mL}$ ) under the same dosing regimen, due to lower body weight in pediatric patients. There were no observed difference in the relationship between concentration of lanadelumab and cHMWK levels between adult and adolescent for both rollover and non-rollover subjects (see section 6.3.1).

#### Immunogenicity

In Study DX-2930-03, the overall incidence of ADA in treated subjects was 11.9% (10/84) of lanadelumab-treated subjects and 4.9% (2/41) of placebo-treated subjects. It seems that the lowest dose of 150 mg Q4W is associated with more ADA incidence. There was no difference in

lanadelumab exposure who were positive or negative for ADA or neutralizing antibodies (See section 6.3.1).

## Pharmacodynamics

Overall, the cHMWK levels decrease with increasing concentrations of lanadelumab. The maximum reduction in cHMWK was observed with chronic dosing regimen 300 mg Q2W, leading to numerically better HAE control with respect to HAE attack reduction. There was no observed difference in the relationship between concentration of lanadelumab and cHMWK levels between adults and adolescents.

### 6.2.2. General Dosing and Therapeutic Individualization

#### General Dosing

Clinical Pharmacology properties of lanadelumab support the following proposed dosing regimen in patients with HAE aged 12 years and older:

Lanadelumab should be administered subcutaneously. Maximal efficacy was observed at doses of 300 mg Q2W and is the recommended starting dose. Patients may consider tapering down to 300 mg Q4W after (b) (4) months. The recommended dose was supported by the two phase 3 studies (DX-2930-03 and DX-2930-04). See section 6.1 and 6.3.2 for details.

#### Therapeutic Individualization

No dose adjustment is recommended in specific populations, with respect to sex, body weight, age, race, renal or hepatic function (See section 2.7.1).

#### Outstanding Issues

None.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Lanadelumab is a recombinant, fully human IgG1 $\kappa$  monoclonal antibody that binds plasma kallikrein and inhibits its proteolytic activity. The molecular mass of lanadelumab based on the amino acid sequence of the assembled IgG composed of both light and heavy chains is (b) (4) Daltons.

Drug product: Lanadelumab drug product is a sterile preservative-free solution for subcutaneous administration at a concentration of 150 mg/mL and is provided in (b) (4) dosage strength (b) (4) 300 mg. The commercial formulation was used in the Phase 3 Studies.

**Pharmacokinetics of lanadelumab**

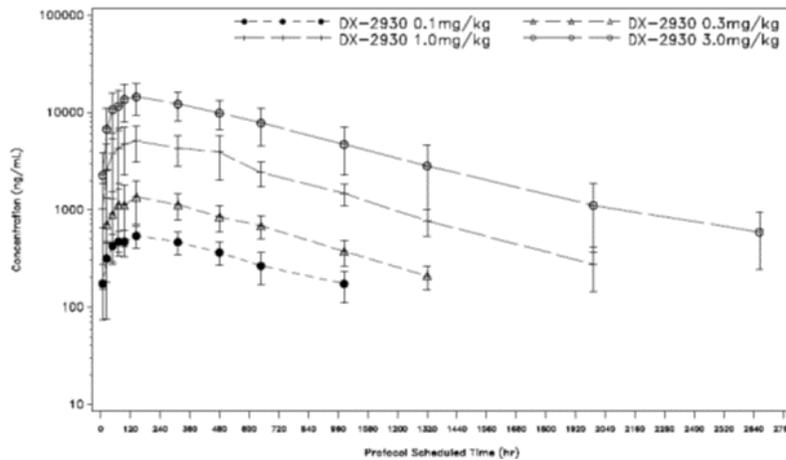
The PK properties of lanadelumab were investigated in a single-ascending dose placebo controlled Phase 1a study, a multiple-ascending dose placebo-controlled Phase 1b study, a double-blind, placebo-controlled Phase 3 study, and an open-label Phase 3 extension study:

PK in healthy subjects

In a single dose study in healthy adults (Study DX-2903-01), lanadelumab PK was characterized following sequential, ascending dose cohorts: 0.1, 0.3, 1.0, or 3.0 mg/kg. Study drug (lanadelumab or placebo) was administered by SC injection into the abdomen. The mean plasma concentration-time profile is shown in Figure 2. PK parameters are summarized in Table 18.

Following SC administration, maximum plasma concentration of lanadelumab was reached at around 5-7 days post dose. The terminal half-life was 2-3 weeks, consistent across the dose groups after single dose subcutaneous administration. Lanadelumab appears to follow one compartmental disposition kinetics with parallel elimination phases across dose groups.

**Figure 2. Mean Lanadelumab Plasma Concentrations in Healthy Subjects Pharmacokinetic Population (Study DX-2930-01)**



Source: Figure 2, Summary of clin pharm

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Takhzyro (lanadelumab)

**Table 18: Summary of Pharmacokinetic Parameters in Healthy Subjects Pharmacokinetic Population (Study DX-2930-01)**

Dose Group	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (day)	AUC <sub>0-48h</sub> (ng <sup>2</sup> h/mL)	AUC <sub>0-inf</sub> (ng <sup>2</sup> h/mL)	CL/F (mL/h)	Vd <sub>f</sub> /F (L)	t <sub>1/2</sub> (day)
0.1 mg/kg							
n	6	6	6	6	6	6	6
Mean	555.0	6.02	373430.3	479944.2	18.22	12.094	20.6
SD	123.85	3.851	121743.21	163272.39	8.837	3.5315	4.30
0.3 mg/kg							
n	6	6	6	5 <sup>a</sup>	5 <sup>a</sup>	5 <sup>a</sup>	5 <sup>a</sup>
Mean	1370.8	7.19	798743.7	1068787.9	25.82	14.986	16.8
SD	626.96	2.858	465168.83	356655.29	9.332	5.2931	1.87
1.0 mg/kg							
n	6	6	6	6	6	6	6
Mean	5611.7	7.55	4073423.9	4174640.2	19.55	11.958	17.6
SD	2422.30	6.265	1383502.62	1386672.49	11.022	7.9312	3.93
3.0 mg/kg							
n	6	6	6	6	6	6	6
Mean	14548.3	5.68	12435165.5	12856569.3	23.15	16.371	21.2
SD	5224.10	0.821	5068346.60	5370654.93	12.238	9.1768	5.08

Source: Table 2, summary of clin pharm

#### PK in HAE patients

Multiple dose PK of lanadelumab was characterized in subjects with HAE in a multiple-ascending dose, placebo-controlled Phase 1b study (DX2930-02), a double-blind, placebo-controlled Phase 3 study (DX2930-03), and an open-label Phase 3 extension study (DX2930-04). Lanadelumab PK after multiple doses was consistent with the single dose PK.

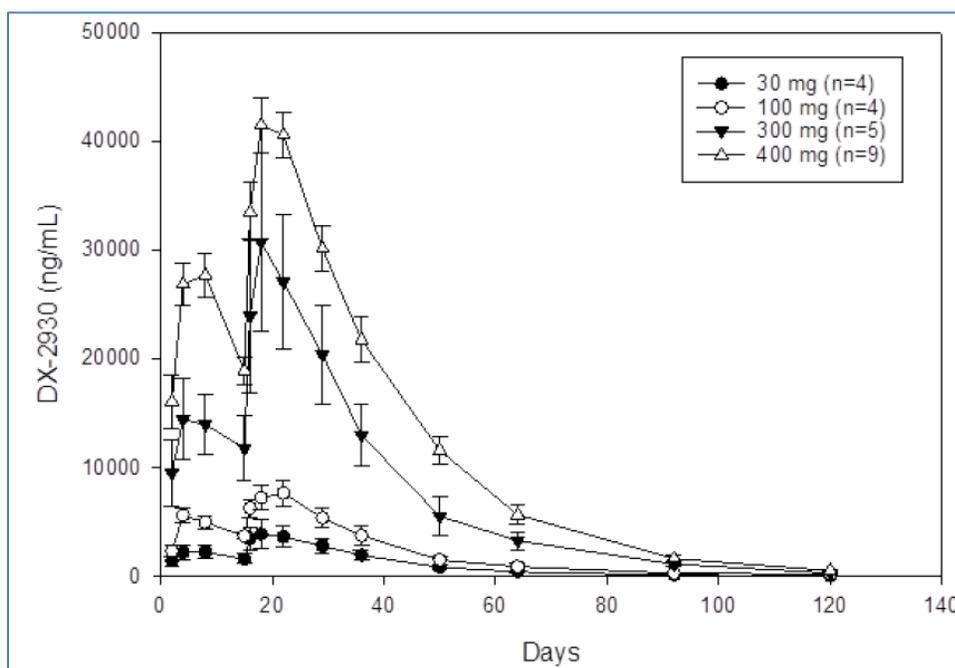
In the phase 1b study, subjects aged at least 18 years were randomized to receive either active study drug or placebo within one of the following cohorts: 30, 100, or 300 mg; a flexible dose-escalation scheme was used in this study that also allowed for an additional 400 mg dose cohort. Two doses of study drug (lanadelumab or placebo), separated by 14 days, were administered by SC injection into the upper arm. The PK profile showed linear, dose-dependent drug exposure up to 400 mg. The median T<sub>max</sub> was about 4-5 days post last dose (Table 19, last dose at day 14) and mean apparent terminal t<sub>1/2</sub> was about two weeks. Mean plasma PK profiles are shown in Figure 3 and summary PK parameters are listed in Table 19.

**Table 19: Lanadelumab serum pharmacokinetic parameters**

Dose Group	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (day)	AUC (day*ng /mL)	CL/F (L/day)	Vd/F (L)	t <sub>1/2</sub> (day)
30 mg (n=4)						
Mean	3895.0	17.9	64,100.0	0.572	11.6	14.2
SD	2159.76	1.14	34,731.16	0.2683	4.92	0.83
100 mg (n=4)						
Mean	7890.0	18.0	135,425.0	0.811	16.1	14.6
SD	2058.43	0.46	48,616.76	0.2826	2.69	3.41
300 mg (n=5)						
Mean	27,460.0	18.2	451,800.0	1.004	17.4	13.8
SD	14,542.46	1.45	226,801.01	0.9087	10.56	3.25
400 mg (n=9)						
Mean	45,322.2	17.7	762,777.8	0.551	11.7	15.0
SD	8704.56	0.98	166,713.66	0.1432	2.76	2.44

Source: Table 4, summary of clin pharm

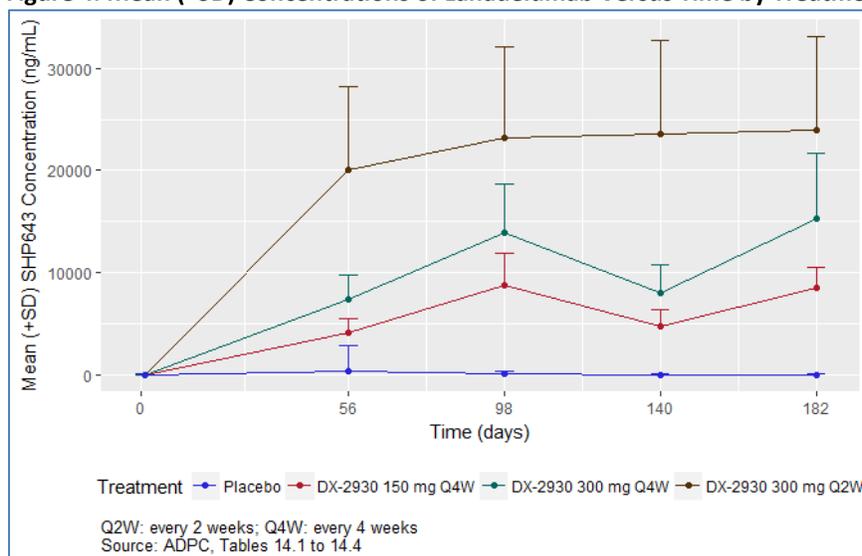
**Figure 3. Mean Lanadelumab Plasma Concentrations in Subjects with HAE Pharmacokinetic Population (Study DX-2930-02)**



Source: Figure 1, study report DX2930-02

PK samples were collected at day 0, 56, 98, 140, and 182 in the Phase 3 study (Study DX2930-03). As shown in Figure 4, lanadelumab concentrations increased with increasing dosage regimens. All PK samples were collected at pre-dose (C<sub>trough</sub>) for the Q2W dosing regimen. It appears that based on the C<sub>trough</sub> from 300 mg Q2W arm, the steady state was achieved between Days 56 and 98. The fluctuating concentrations observed in the Q4W dosing regimens are due to PK sampling at different nominal times related to the dosing interval. For Q4W dosing regimens, Day 98 and 182 were 14 days post dose, and the Day 0, 56, and 140 would represent C<sub>trough</sub>.

**Figure 4. Mean (+SD) Concentrations of Lanadelumab Versus Time by Treatment Over Treatment Period**



Source: Figure 27, study report DX2930-03

Based on population PK analysis, the anticipated population time to reach steady state concentration was approximately 70 days. At steady-state, the mean accumulation ratio is approximately 1.44, 1.42, and 2.43 for dosing regimen of 150 mg Q4W, 300 mg Q4W and 300 mg Q2W, respectively.

**Table 20: Descriptive Statistics of PK Parameters of lanadelumab**

Regimen	Descriptive Statistics	CL/F (L/h)	Vc/F (L)	AUC <sub>tau,ss</sub> (µg.day/mL)	C <sub>ave,ss</sub> (ng/mL)	C <sub>max,ss</sub> (ng/mL)	C <sub>min,ss</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)
150 mg Q4W	n	28	28	28	28	28	28	28	28
	Mean	0.0272	13.3	235	8390	12600	4660	108	345
	CV%	22.7	16.8	23.5	23.5	22.4	28.5	10.9	11.5
	Geo Mean	0.0265	13.1	229	8170	12300	4480	108	343
	Geo CV%	23.2	17.5	23.3	23.3	21.9	28.8	10.9	11.5
	Median	0.027	13.6	225	8040	12300	4460	102	344
	Minimum	0.0167	9.24	147	5240	8430	2470	93.7	274
	Maximum	0.0413	18.2	357	12700	18900	7490	124	438
300 mg Q4W	n	29	29	29	29	29	29	29	29
	Mean	0.0319	14.9	417	14900	22600	8110	112	331
	CV%	31.0	24.2	27.7	27.7	27.6	30.8	9.8	10.9
	Geo Mean	0.0306	14.5	403	14400	21800	7700	111	329
	Geo CV%	29.4	24.1	29.2	29.2	28.1	35	10.2	11.3
	Median	0.0288	14	421	15100	22600	8330	119	330
	Minimum	0.0168	7.86	213	7600	12000	2900	94.2	233
	Maximum	0.0591	24.4	729	26100	41500	13600	122	410
300 mg Q2W	n	27	27	27	27	27	27	27	27
	Mean	0.0341	15.9	398	28400	35000	24100	87.9	335
	CV%	46.8	33.6	34.4	34.4	34.2	35.2	13	9.5
	Geo Mean	0.0315	15.1	373	26600	32800	22500	87.1	333
	Geo CV%	40.4	30.5	40.6	40.6	40.1	41.8	13.5	10
	Median	0.029	13.6	409	29200	36100	24400	95.1	344
	Minimum	0.0176	9.7	131	9350	11700	7640	71.3	258
	Maximum	0.0879	32.7	667	47600	58500	41200	98.8	382

Source: Table 5, Part 1 of pop PK report

### Absorption

The pharmacokinetic properties and exposure (steady state) of lanadelumab were

characterized in HAE subjects, following subcutaneous administration of 150 mg Q4W, 300 mg Q4W and 300 mg Q2W (Table 20). The median  $t_{max}$  was observed in 4 to 5 days. The anticipated population time to reach steady state concentration was approximately 70 days.

#### *Distribution*

In patients with HAE, the apparent volume of distribution at steady state was 13.3-15.9 L.

#### *Metabolism*

The metabolic pathway of lanadelumab has not been characterized. As a monoclonal antibody lanadelumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

#### *Elimination*

From population pharmacokinetic analysis, lanadelumab exhibited linear pharmacokinetics and no evidence of target receptor-mediated elimination.

#### Intrinsic factors/Specific populations

Population pharmacokinetic analyses showed that age, gender and race did not meaningfully influence the pharmacokinetics of lanadelumab 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  $C_{max}$ ) in lighter patients. However, this difference is not considered to be clinically relevant and no dose adjustments are recommended for any of these demographics.

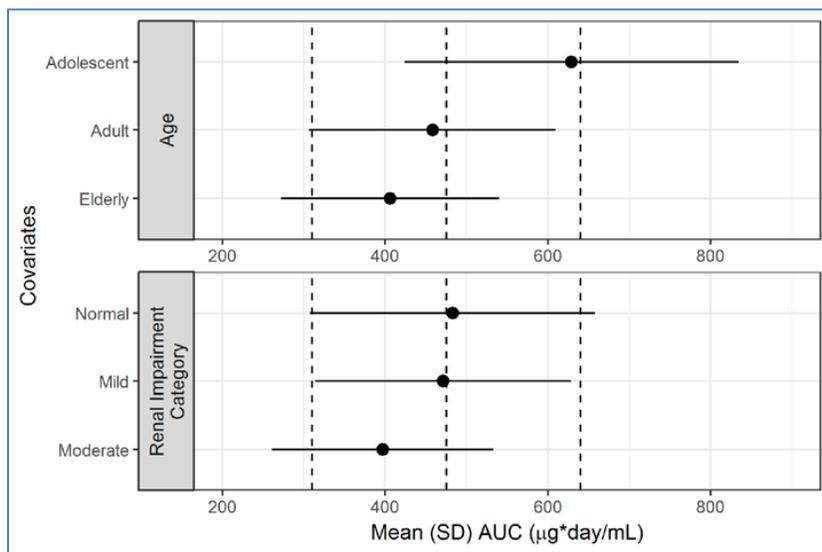
#### *Pediatric Population*

Based on post-hoc analyses in Study DX-2930-04, PK parameters for adolescents (12 to 17 years, N=21) and adults (18 to 65 years, N=180) are presented in Figure 5. No influence of age was apparent on CL/F of lanadelumab after correcting for body weight. Based on mean post-hoc PK parameters estimated, an approximately 37% higher exposure ( $AUC_{tau,ss}$ ) was observed in adolescents compared to adults (18 to 65 years). There was no observed difference in the relationship between concentration of lanadelumab and cHMWK levels in adult and adolescent subjects. Based on the PK, efficacy and safety (See section 8.1.1), no dose adjustment is recommended for adolescents (12 to 17 years).

#### *Renal Impairment*

No dedicated studies have been conducted to evaluate the PK of lanadelumab in renal impairment patients. Based on post-hoc analyses, mean ( $\pm$ SD)  $AUC_{tau,ss}$  of lanadelumab according to renal function are presented in Figure 5. Based on population pharmacokinetic analysis, renal impairment (estimated GFR: 60 to 89 mL/min/1.73m<sup>2</sup>, [mild, N=98] and 30 to 59 mL/min/1.73m<sup>2</sup>, [moderate, N=9]) had no effect on the clearance or volume of distribution of lanadelumab. No dose adjustment is required.

**Figure 5. Mean ( $\pm$ SD) AUC<sub>tau,ss</sub> of Lanadelumab According to Age and Renal Impairment Category in Study DX-2930-04 (Rollover and Non-rollover Subjects Combined)**

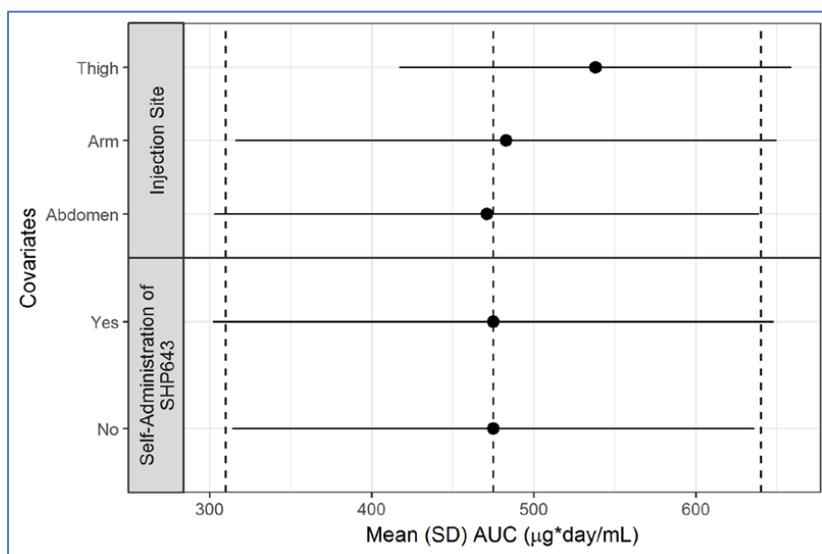


\*Vertical dashed lines are the mean AUC<sub>tau,ss</sub> (475 µg\*h/day) and  $\pm$  standard deviation (165 µg\*h/day) in the overall population.  
Source: Figure 8, Part 2 of pop PK report

#### *Effect of Body Site Injection and Self-Administration on Pharmacokinetics*

As showed in Figure 6, PK properties and exposure between body site injection (upper arm, thigh or abdomen) were comparable to observed PK parameters in Study DX-2930-03 (upper arm). These data confirmed no effect of body site injection on PK of lanadelumab, supporting that body site injection of upper arm, thigh or abdomen will appropriately deliver the desired exposure of lanadelumab.

**Figure 6. Mean ( $\pm$ SD) AUC<sub>tau,ss</sub> of Lanadelumab According to Body Site Injection and Type of Administration in Study DX-2930-04 (Rollover and Non-rollover Subjects Combined)**



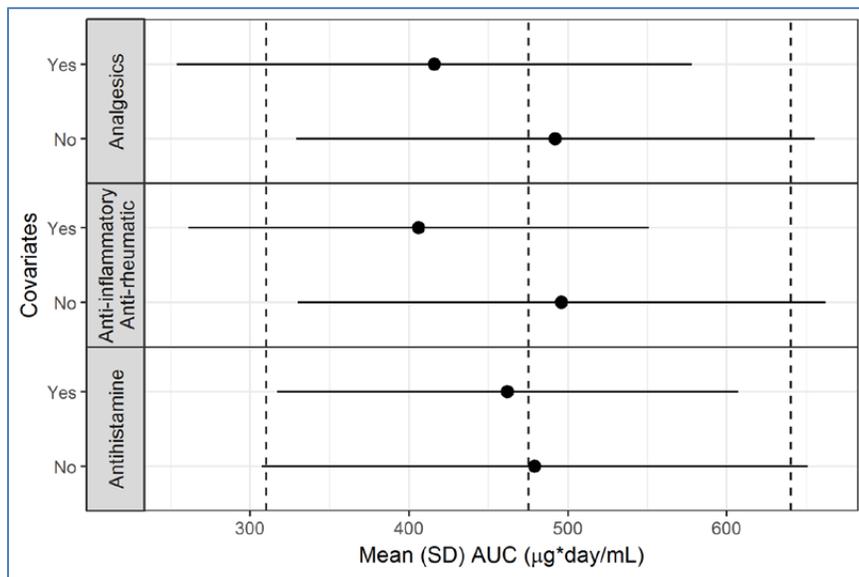
\*Vertical dashed lines are the mean AUC<sub>tau,ss</sub> (475 µg\*h/day) and  $\pm$  standard deviation (165 µg\*h/day) in the overall population.  
Source: Figure 9, Part 2 of pop PK report

### Extrinsic factors

#### *Drug interaction*

The use of analgesic, antibacterial, antihistamine, anti-inflammatory and anti-rheumatic medications had no effect on clearance and volume of distribution of lanadelumab (Figure 7). For breakthrough HAE attacks, use of rescue medications such as plasma-derived and recombinant C1-INH, icatibant or ecallantide had no effects on clearance and volume of distribution of lanadelumab.

**Figure 7. Mean ( $\pm$ SD) AUC<sub>tau,ss</sub> of Lanadelumab According to Concomitant Medication Use (Rollover and Non-rollover Subjects Combined)**



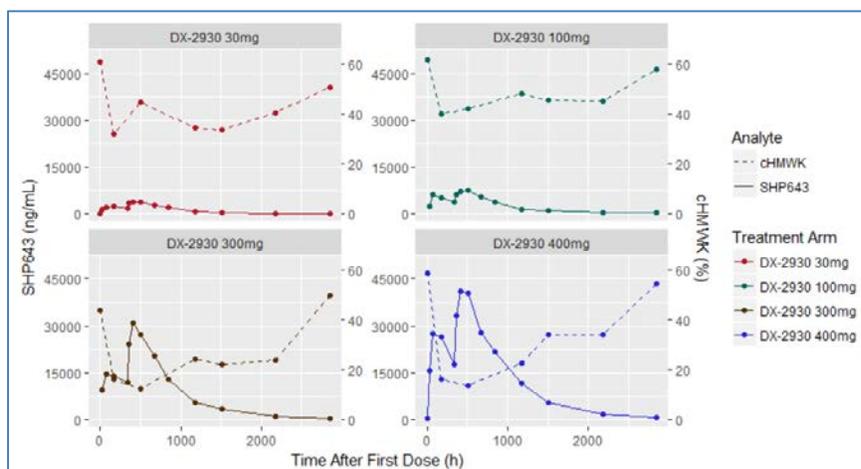
\*Vertical dashed lines are the mean AUC<sub>tau,ss</sub> (475 µg\*h/day) and  $\pm$  standard deviation (165 µg\*h/day) in the overall population.  
Source: Figure 10, Part 2 of pop PK report

### **Pharmacodynamics**

#### *Effects on cHMWK levels*

In the phase Ib study DX2930-02, cHMWK levels were reduced by day 7 following the first administration. cHMWK levels were further reduced by the second dose. Lanadelumab (aka SHP643) doses of 300 and 400 mg (administered 14-days apart) resulted in a similar suppression of cHMWK levels (%) suggesting a plateauing of effect. Mean cHMWK (%) levels slowly returned to baseline approximately 110 days (2600 h) after first dose (Figure 8).

Figure 8. Mean Concentration-Time Profiles of Lanadelumab and cHMWK (DX-2930-02)

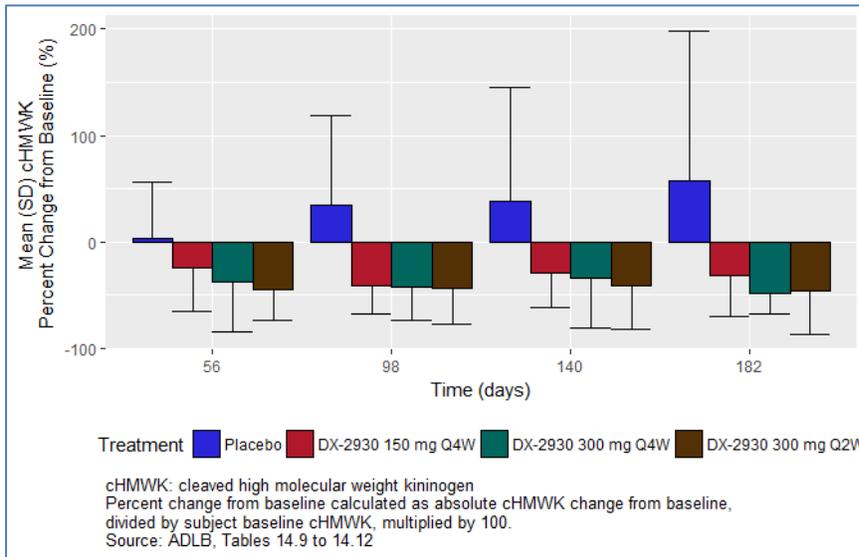


Source: Figure 9, Part 1 of Pop PK report

Consistent with the phase Ib study, the cHMWK levels decrease with increasing concentrations of lanadelumab in the Phase III study. The plasma obtained from the subjects 56 days, 98 days, 140 days, and 182 days after the first dose (Day 0) during the treatment period had a significantly lower mean percentage cHMWK, and the maximum reduction in cHMWK was observed with chronic dosing regimen 300 mg Q2W. After chronic and continuous administration, a sustained decrease in cHMWK was observed by 8 weeks after initiation of therapy for all dosing regimens (1324 h, Figure 10).

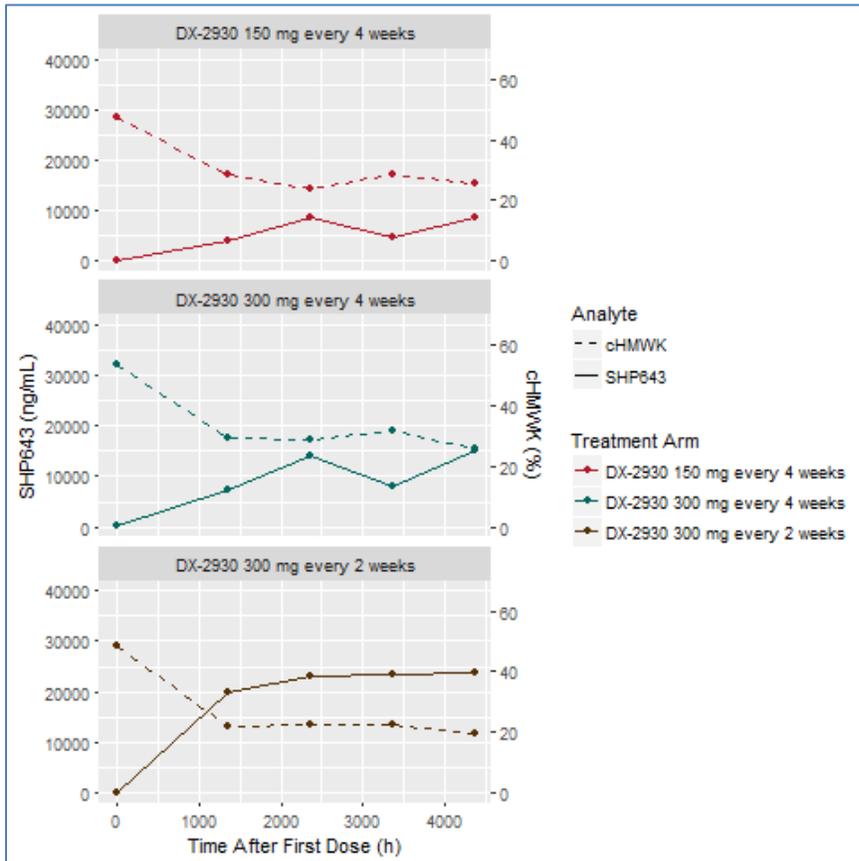
Based on simulation (Figure 11), time to reach 95% steady-state cHMWK levels (%) levels for the Q2W and Q4W regimens were reached after 14 and 56 days of treatment, respectively (corresponding to the 1st dose administered for Q2W and the 2nd dose for Q4W). Time to reach 99% steady-state cHMWK levels (%) for the Q2W and Q4W regimens were observed after 14 and 84 days of treatment, respectively (corresponding to the 1st dose for the Q2W and 3rd dose for Q4W regimens). The estimated time for cHMWK values to return to within 5% of baseline following the last dose for the 150 mg q4wk, 300 mg q4wk and 300 mg q2wk regimens were approximately 139, 154 and 163 days, respectively, suggesting the inhibition of cHMWK was reversible.

**Figure 9. Mean (+SD) Percent Change From Baseline Levels of cHMWK Versus Time by Treatment Over Treatment Period**



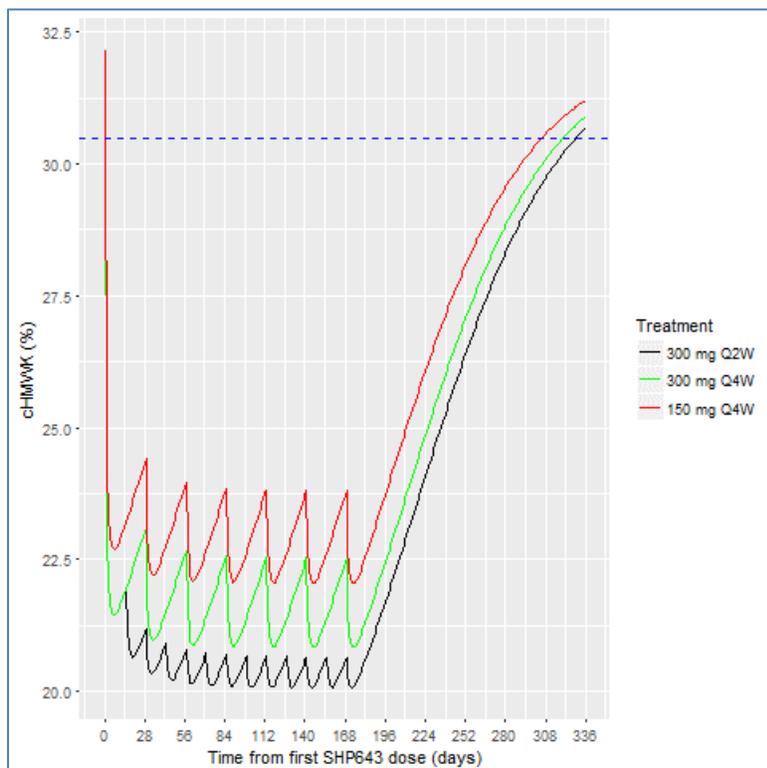
Source: Figure 29, Study report DX-2930-03

**Figure 10. Observed Mean Concentration-Time Profiles of SHP643 and cHMWK (DX-2930-03)**



Source: Figure 10, Part 1 of Pop PK report

**Figure 11. Time to Return to Baseline of cHWMK (%) Level after Stopping Treatment of SHP643 Dosing (150 mg Q4W, 300 mg Q4W and 300 mg Q2W)**



Source: Figure 15, Pop PK report Part 2

### *Effects on QT*

No dedicated thorough QT/QTc prolongation and proarrhythmic potential study has been conducted for lanadelumab. Lanadelumab is a monoclonal antibody; the ability of monoclonal antibodies to cause QT effect via indirection mechanisms is minimal. Based on totality of the clinical program with sufficient assessment of ECG at time of maximal exposure, the mechanism of action for the proposed target and indication, and indicated population, lanadelumab did not prolong the QT/QTc interval.

### *Immunogenicity*

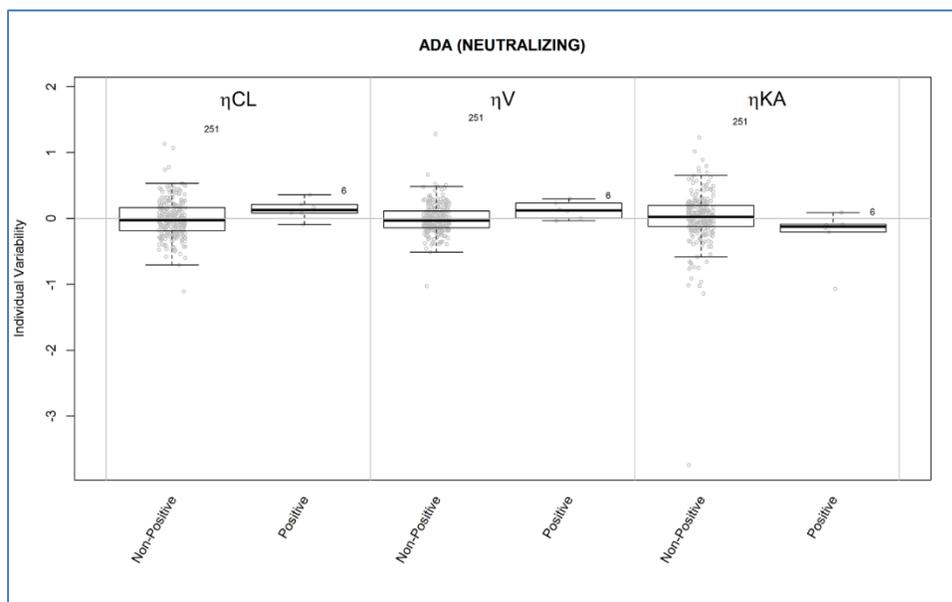
In Study DX-2930-03, the overall incidence of ADA in treated subjects was 11.9% (10/84) of lanadelumab-treated subjects and 4.9% (2/41) of placebo-treated subjects. It seems that the lowest dose of 150 mg Q4W is associated with more ADA incidence (Table 21). In the open label study, the overall prevalence of ADAs in treated subjects was 9.0% (19 of 212 subjects). A total of 6 subjects (2.8%, 6 of 212) on the study developed neutralizing ADAs. There was no difference in lanadelumab exposure (Figure 12), cHWMK levels, and efficacy/safety for subjects who were positive or negative for ADA or neutralizing antibodies.

**Table 21: Summary of Immunogenicity Response - Study DX-2930-03 Safety Population**

Parameter	Placebo N=41 n (%)	Lanadelumab			Total N=84 n (%)
		150 mg q4wks N=28 n (%)	300 mg q4wks N=29 n (%)	300 mg q2wks N=27 n (%)	
ADA prevalence <sup>a</sup>	3 (7.3)	5 (17.9)	3 (10.3)	4 (14.8)	12 (14.3)
ADA incidence <sup>b</sup>	2 (4.9)	5 (17.9)	3 (10.3)	2 (7.4)	10 (11.9)
Pre-existing ADA <sup>c</sup>	1 (2.4)	0 (0.0)	1 (3.4)	2 (7.4)	3 (3.6)
Treatment-induced <sup>d</sup>	2 (4.9)	5 (17.9)	2 (6.9)	2 (7.4)	9 (10.7)
Treatment-boosted <sup>e</sup>	0 (0.0)	0 (0.0)	1 (3.4) <sup>f</sup>	0 (0.0)	1 (1.2)
Non-neutralizing ADA	3 (7.3)	3 (10.7)	3 (10.3)	4 (14.8)	10 (11.9)
Neutralizing ADA	0 (0.0)	2 (7.1)	0 (0.0)	0 (0.0)	2 (2.4)

Source: Table 64, summary of clin safety

**Figure 12. Positive ADA (Neutralizing) effect on PK parameters.  $\eta$ CL: Random Effect on Clearance;  $\eta$ KA: Random Effect on Absorption Rate;  $\eta$ V: Random Effect on Central Volume of Distribution**



Source: Figure 11.12, Pop PK report Part 2

### 6.3.2. Clinical Pharmacology Questions

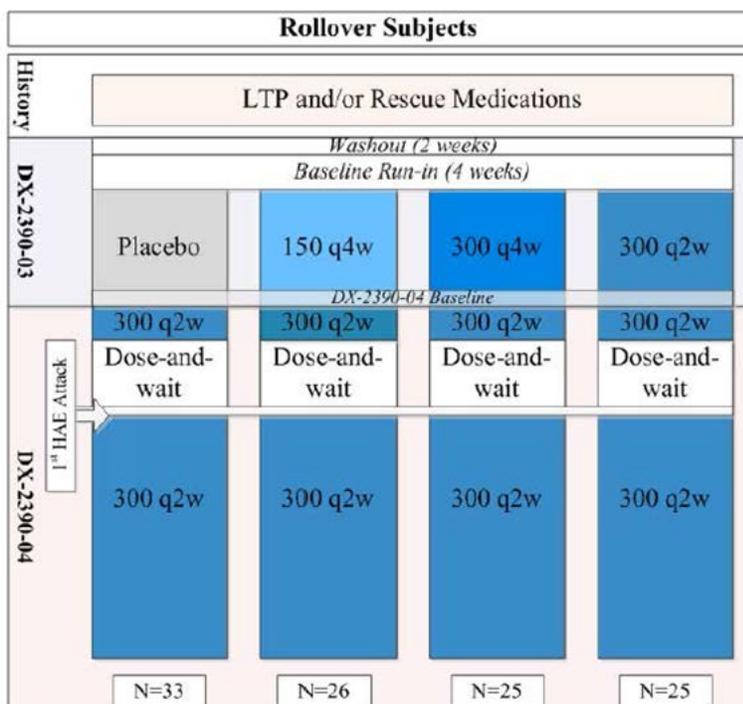
#### Does the clinical pharmacology program provide supportive evidence of effectiveness?

BLA761090 consists of two Phase 1 studies that were conducted in healthy adults (Study DX-2930-01) or adults with HAE (Study DX-2930-02). Two Phase 3 studies were conducted in subjects aged 12 years and older with HAE, including a double-blind, placebo-controlled Phase 3 study (DX2930-03), and an open-label Phase 3 extension study (DX2930-04): Three dosing regimens (150 mg Q4W, 300 mg Q4W, 300 mg Q2W) were assessed for the proposed indication in the pivotal Phase 3 study (DX-2930-03).

The pivotal evidence for dose recommendation is based on efficacy/safety data from study DX-2930-03 and data from rollover patients in study DX-2930-04. Phase 3 study design is described in Figure 13.

For assessment of the primary and secondary endpoint in the pivotal study, please see section 8.

**Figure 13. Study design for rollover subjects**



Source: Figure 3, study report DX-2930-04

**Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

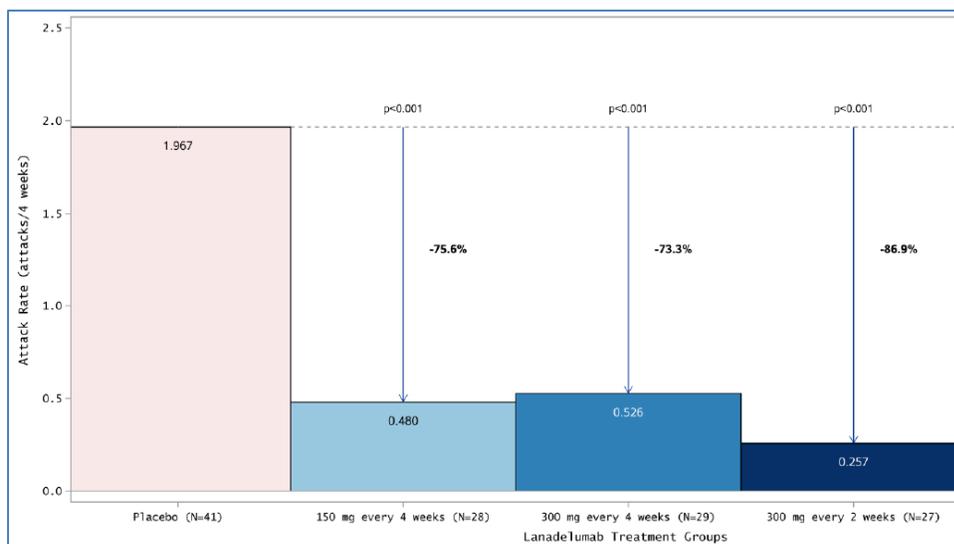
In general, the proposed dose of 300 mg q2w is a reasonable starting dose from a clinical pharmacology perspective. A dosing interval of 300 mg Q4W is also effective and may be considered in those patients well-controlled after (b) (4) 6 months. The exposure response for efficacy and safety supports the dosing recommendation:

**Efficacy**

The Applicant studied three dosing regimens in the double-blind phase 3 study, and all dosing regimens (300 mg Q2W, 300 mg Q4W, and 150 mg Q4W) were effective compared to placebo. There was no clear dose response in this study. While the 300 mg Q2W resulted in the largest treatment effects (monthly attack rate, time to first attack, attack free rate, see section 8 for details), no clear dose response was observed for 150 mg Q4W and 300 mg Q4W. Consistently,

the lowest dose 150 mg Q4W had similar or numerically better efficacy (attack rate, attack free rate, time to first attack) compared to 300 mg Q4W (Figure 14, also see section 8 for details).

**Figure 14. Poisson Regression of Investigator-Confirmed HAE Attacks During the Treatment Period (Day 0 to Day 182) by Treatment Group-ITT Population**



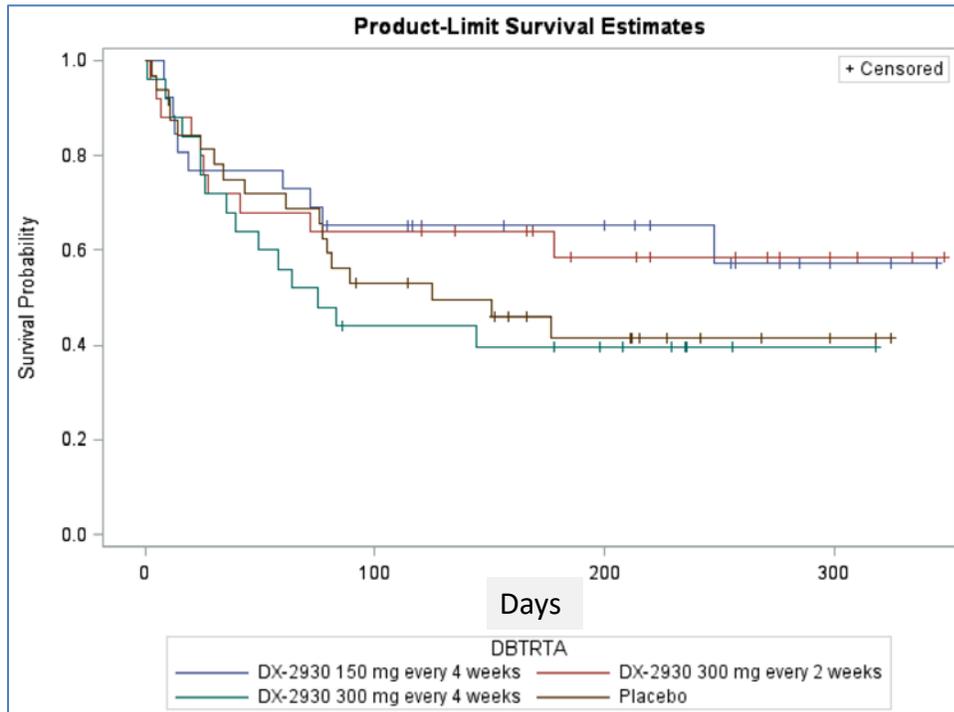
Source: Figure 4, DX2930-3 CSR

The apparent lack of dose response may partially be explained by the limited sample size (~30 patients per arm) and imbalance in patient assignment. Because of the high retention and rollover rates, the OLE allows a comparison of efficacy following the same treatment between patients in different arms. 109 subjects (96.5% of subjects who completed the pivotal study) rolled over into the OLE to receive 300 mg Q2W after the “dose-and-wait” period (Figure 13).

When given the same dose of 300 mg Q2W in study DX2930-04, the patients originally assigned to 300 mg Q4W had the lowest efficacy compared to the patients who were originally assigned to the other three arms (placebo, 150 Q4W, 300 Q2W), as shown in time to first attack analysis (Figure 15), monthly rate analysis (Figure 16), and maximum attack severity analysis (Figure 17).

The lower efficacy observed in patients who were originally assigned to 300 mg Q4W in study DX2930-04 cannot be explained by the treatment difference, as all patients were given the same dosing regimen in the regular dosing stage in study DX-2930-04. The lower efficacy seen in this group cannot be explained by the potential carryover effect, as this group of patients had numerically worse efficacy compared to patients who were originally assigned to placebo. It seems that by chance, more “non-responders” were randomized to the 300 mg Q4W in study 3 (Figure 18).

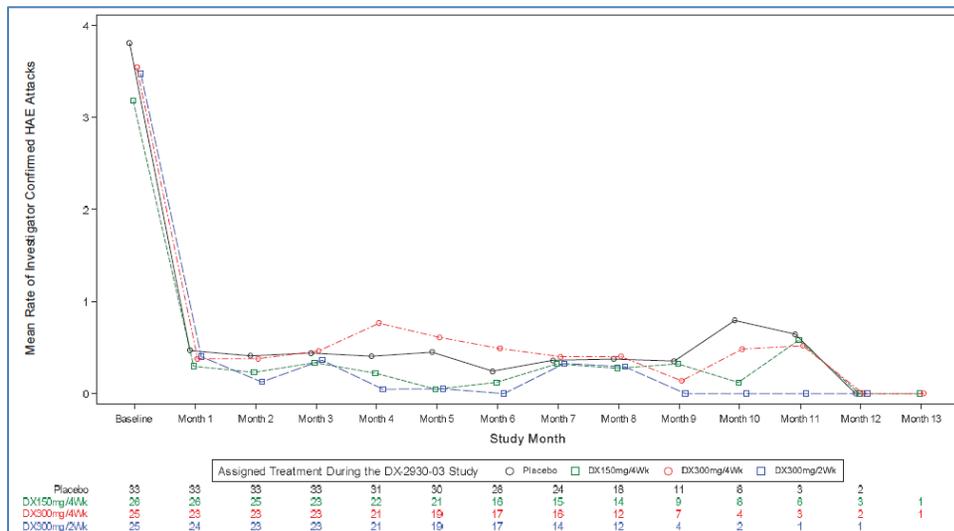
**Figure 15. Time to First Investigator-Confirmed Attack Day 0 to Day 182 (rollover population, regular dosing stage) in Study DX-2930-04**



\*All patients were on treatment of lanadelumab 300 mg Q2W. Patients were grouped by their previously assigned treatment in Study DX-2030-03.

Source: reviewer analysis

**Figure 16. Number of Investigator-confirmed HAE Attacks per Month During the Regular Dosing Stage of the Treatment Period (Rollover Safety Population)**

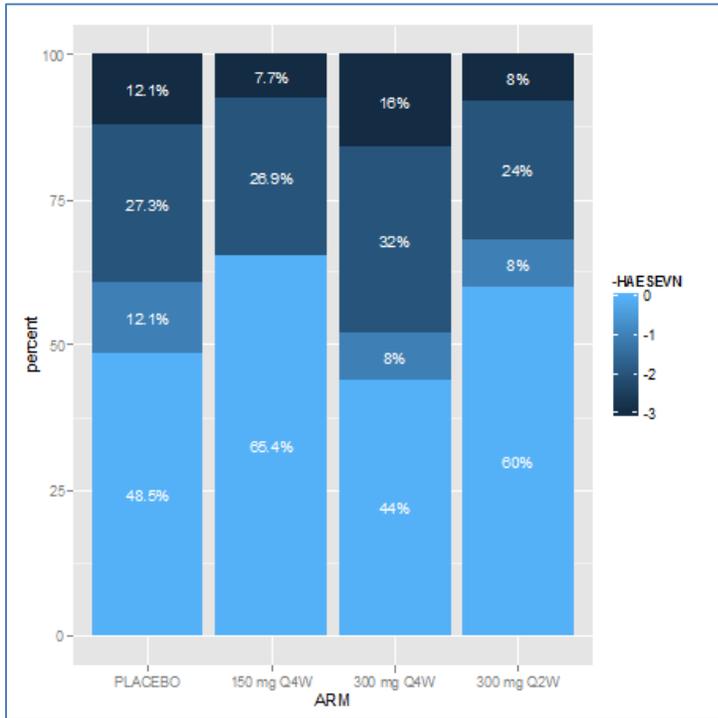


\*Patients were grouped by their previously assigned treatment in Study DX-2030-03.

Source: Figure 14.2.6.1.2

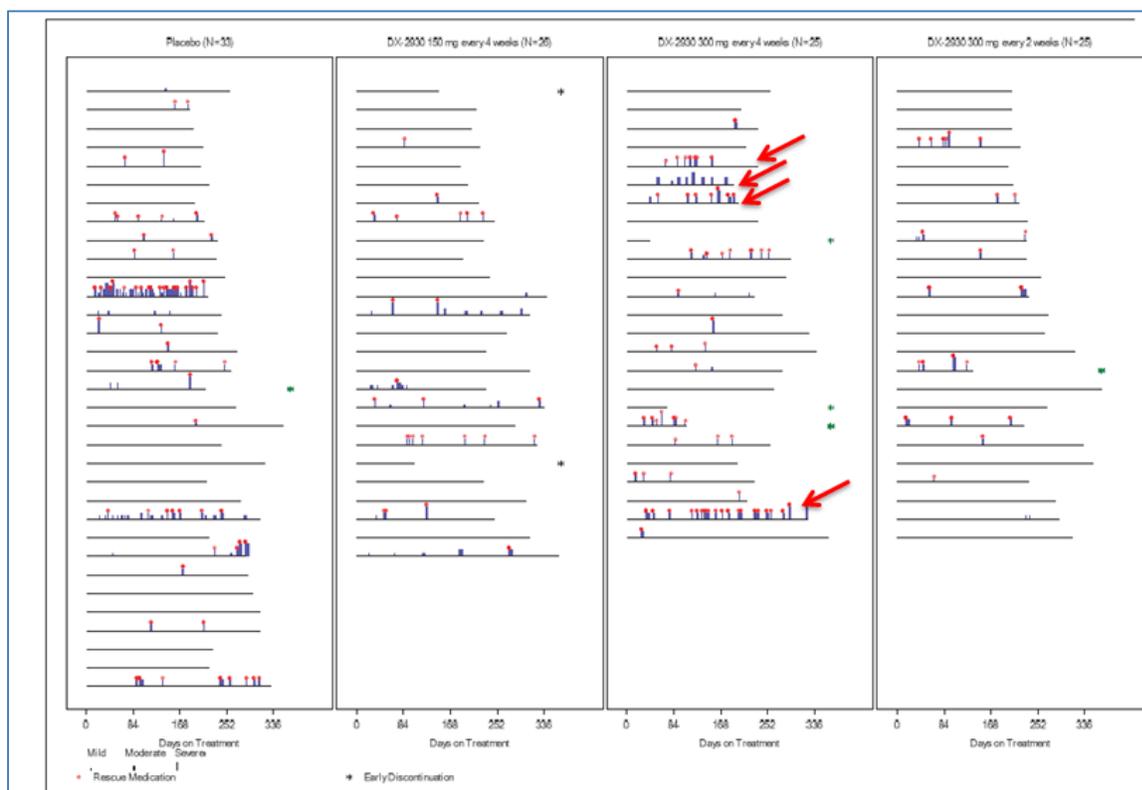
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Figure 17. Maximum HAE Attack Severity During the regular dosing stage (Day 0 to Day 182) in Study DX-2930-04



\*All patients were on treatment of lanadelumab 300 mg Q2W. Patients were grouped by their assigned treatment in Study DX-2030-03. (Note: Maximum HAE attack severity is the most severe attack reported by the subject. HAESEVN: 0-no attack, 1-mild, 2-moderate, 3-severe)  
Source: reviewer analysis

**Figure 18. All HAE Attacks During the Regular Dosing Stage of the Treatment Period (Rollover Safety Population)**



\*All patients were on treatment of lanadelumab 300 mg Q2W. Patients were grouped by their assigned treatment in Study DX-2030-03. More “non responders (highlighted by red arrows)” were observed in patients who were originally assigned to 300 mg q4w arm.  
Source: Figure 14.2.2.2, Study report DX2930-04

### FDA analysis to compare efficacy after dose escalation

While dose titration was not formally evaluated in the lanadelumab development program, the results from the OLE allowed us to compare efficacy between treatments within the same patients. A total of 84 rollover subjects switched dosing regimens after the transition from Study DX2930-03 to the OLE: 33 placebo subjects, 26 subjects on 150 mg Q4W, and 25 subjects on 300 Q4W all switched to 300 mg Q2W. For these three groups of subjects, this represented an increase in the total monthly dose and dosing frequency, i.e., from 0 mg, 150 mg Q4W, and 300 Q4W to a total of 600 mg per month (300 mg Q2W). To compare the efficacy before and after dose escalation, we matched efficacy data from study DX2930-03 to the OLE patient population. In other words, we only included rollover patients who received regular Q2W dosing after the ‘dose and wait’ period and matching data at each time point in the comparison (Table 22).

**Table 22: Number of rollover patients in study 4 at each time point**

Month	Placebo	150 mg Q4W	300 mg Q4W	300 mg Q2W	Total
0	33	26	25	25	109
1	33	26	23	24	106
2	33	25	23	23	104

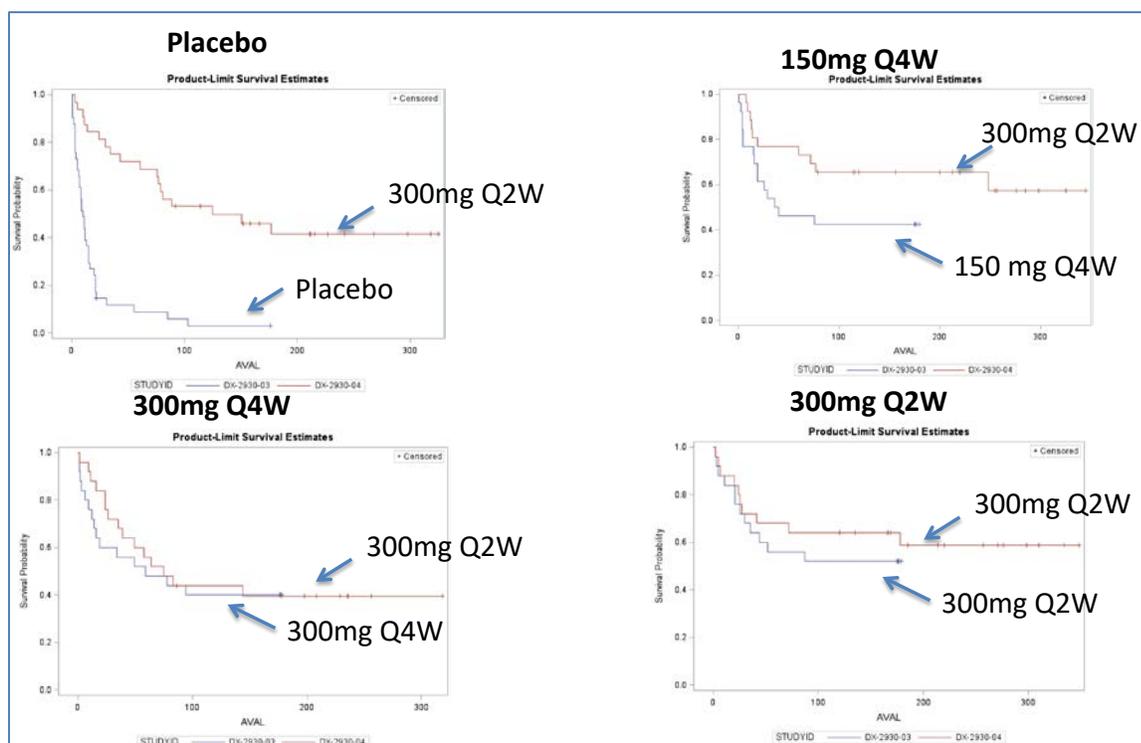
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3	33	23	23	23	102
4	31	22	21	21	95
5	30	21	19	19	89
6	28	16	17	17	78

For rollover patients, there is significant improvement in efficacy after transitioning to 300 mg Q2W for patients originally assigned to placebo and 150 mg q4w arms (Time to first event/Figure 19, monthly attack rate/Figure 20, maximum attack severity/Figure 21, Figure 22). This is consistent with the observed data in Study DX2930-03, where the lanadelumab 300 mg q2w dosing regimen has numerically better efficacy compared to 150 mg q4w in HAE patients.

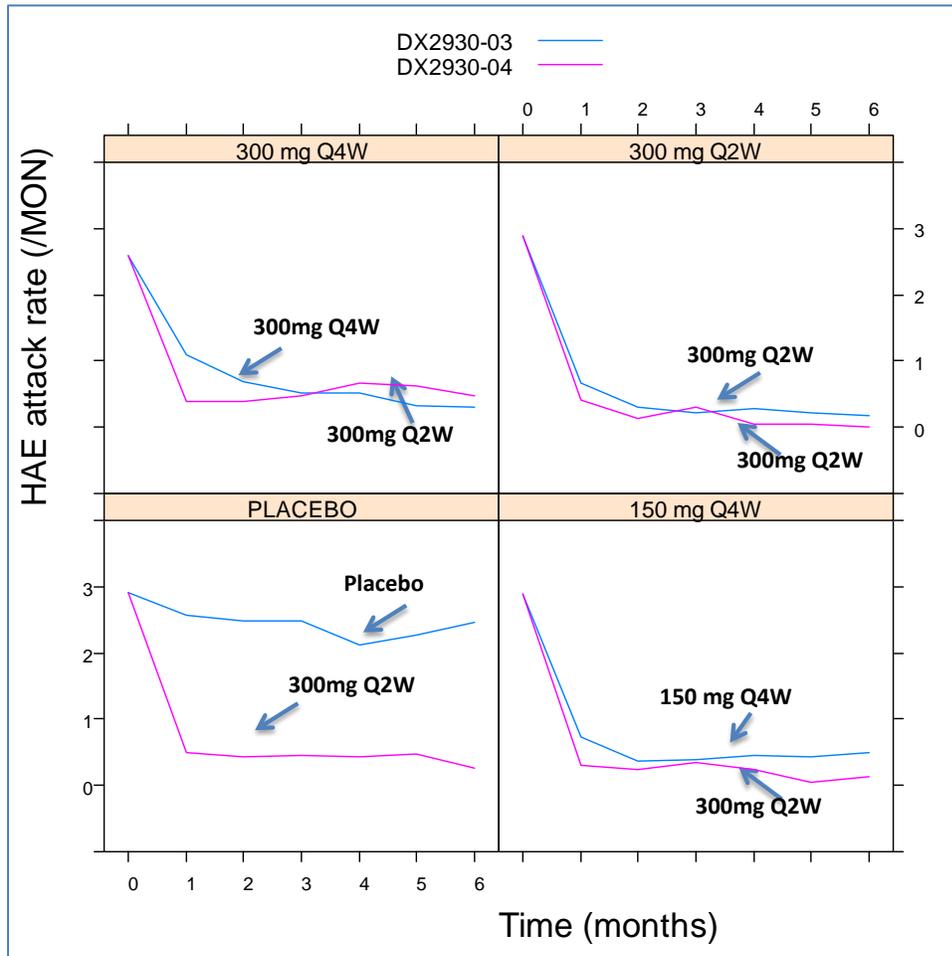
On the other hand, dose escalation from lanadelumab 300 mg Q4W to 300 mg Q2W dosing regimen lead to slightly better efficacy (monthly attack rate, attack free rate, time to first attack) only for the first 3-4 months (Figure 19, Figure 20, Figure 21). After 4 months, the monthly HAE attack rate (Figure 20) and attack free rate (Figure 22) were similar between the two dosing regimens, and the time to first attack (Figure 19) was also similar. Therefore, the Clinical Pharmacology review team recommends the starting dose of 300 mg Q2W, and patients may consider dose reduction to 300 mg Q4W after (4) months.

Figure 19. Time to First Investigator-Confirmed Attack Day 0 to Day 182 (rollover population) in Study DX-2930-03 (blue line) and Study DX-2930-04 (red line), regular dosing stage



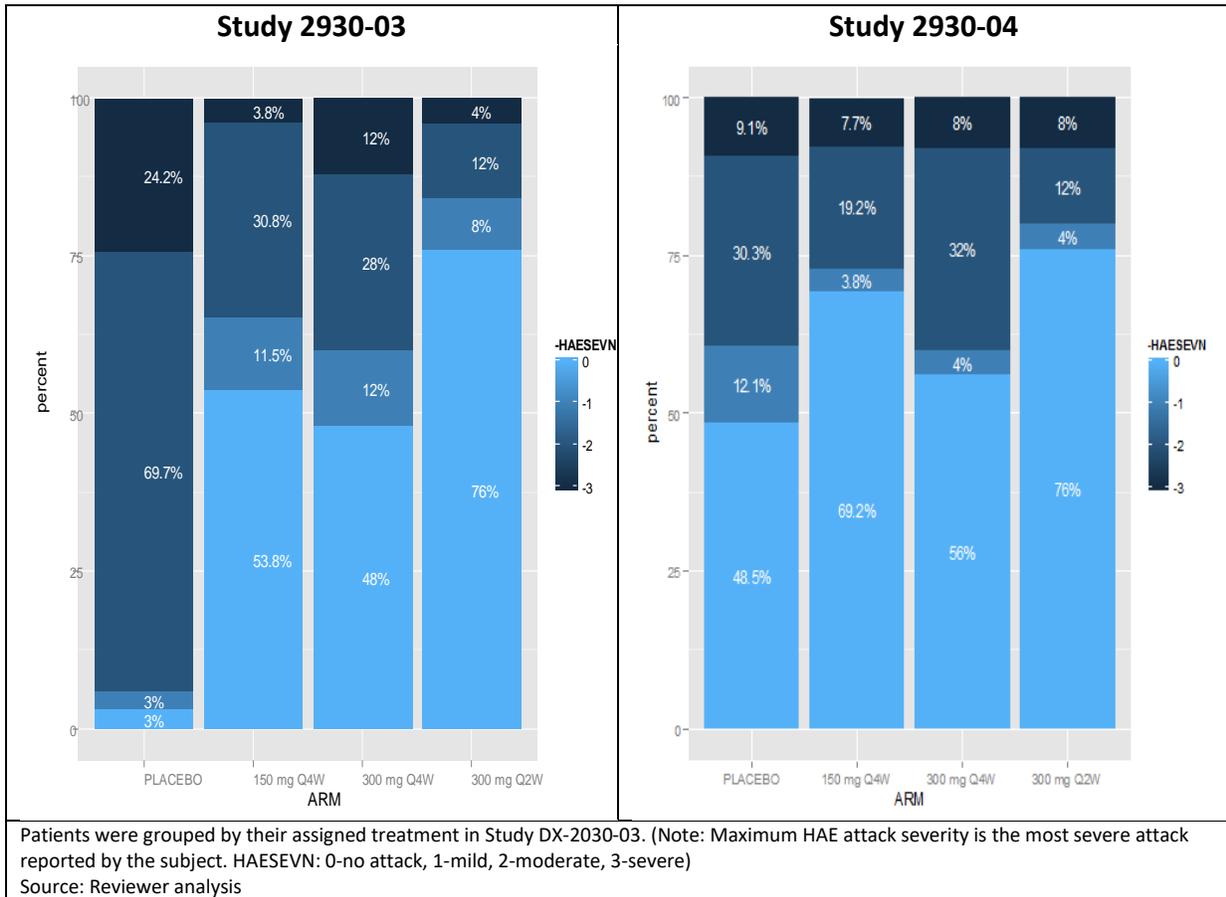
\*Patients were grouped by their assigned treatment in Study DX-2030-03.  
Source: reviewer analysis

Figure 20. Number of Investigator-confirmed HAE Attacks per Month (rollover population) in Study DX-2930-03 (blue line) and Study DX-2930-04 (red line), regular dosing stage

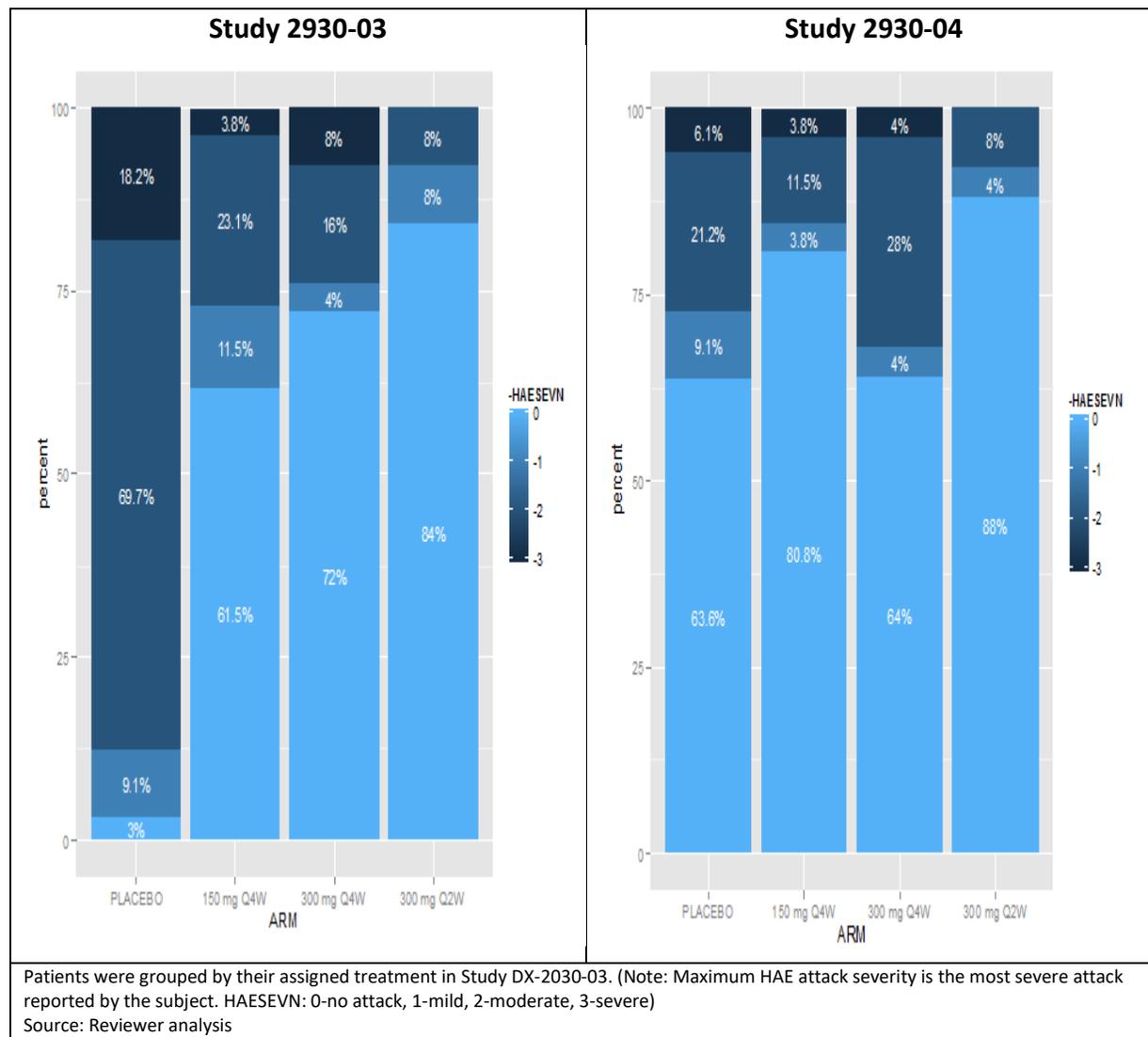


\*Patients were grouped by their assigned treatment in Study DX-2030-03.  
Source: reviewer analysis

**Figure 21. Maximum HAE Attack Severity During the Treatment Period (Day 70 to Day 182) Rollover Population in Study DX-2930-03 and Study DX-2930-04**



**Figure 22. Maximum HAE Attack Severity During the Treatment Period (Day 120 to Day 182) Rollover Population in Study DX-2930-03 and Study DX-2930-04**



**Applicant’s analysis for Study DX-2930-04**

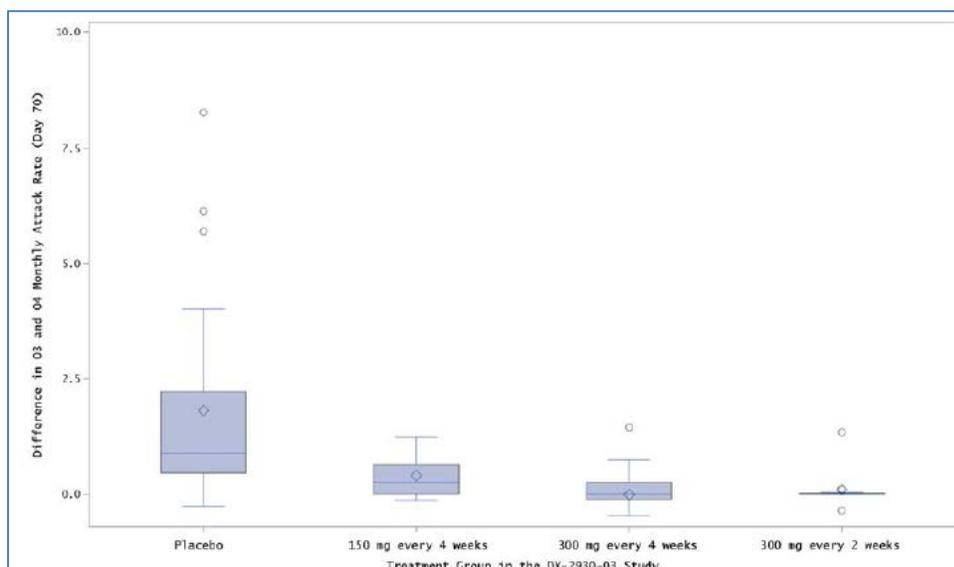
Our analyses described above are consistent with Applicant-conducted post-hoc analyses to explore the impact on efficacy of switching between the dose regimens within the same subject using the within-subject difference in attack rates between DX-2930-03 and the OLE (Figure 23), in which a Wilcoxon signed rank test was used to test if the within-subject difference was different from zero. In order to ensure comparability of the attack rates, the analysis was based on treatment exposure after Day 70 (the estimated steady state) within each study when the subset of 62 subjects would have had at least 4 months (112 days or 16 weeks) of the 182 days regular dosing stage in Study DX-2930-04. The following observations were made:

- Placebo rollover subjects (N=22) showed a significant decrease in attack rate after

transitioning to 300 mg Q2W ( $p=0.001$ ).

- Lanadelumab 150 mg Q4W rollover subjects ( $N=15$ ) showed a significant decrease in attack rate after transitioning to 300 mg Q2W ( $p=0.002$ ).
- Lanadelumab 300 mg Q4W rollover subjects ( $N=13$ ) did not show significant decrease in attack rate after transitioning to 300 mg Q2W ( $p=0.846$ ).
- Most lanadelumab 300 mg Q2W rollover subjects ( $N=12$ ) showed no change in attack rate ( $p=0.625$ ) and remained at a 0 monthly attack rate, demonstrating a durable treatment effect.

**Figure 23. Boxplot of Difference in Monthly Attack Rate between Study DX-2930-03 and Study DX-2930-04 at Steady State in Regular Dosing Stage- Rollover Safety Population**



Source: Figure 21, summary of clin efficacy

Study DX2930-04 was neither blinded nor placebo-controlled, and may introduce bias through unblinding. The sequential design may lead to some carryover effects. Therefore, the conclusions based on the analysis should be interpreted with caution. However, the fact that the efficacy outcome is consistent in study DX2930-03 and study DX2930-04 for the 300 mg Q2W arm, and that the data obtained in the other 3 arms (placebo, 150mg q2w and 300mg q4w) revealed consistent relevant changes with respect to major efficacy endpoints after dose escalation attest to the validity and clinical relevance of the data from this open-label study. Although the number of patients studied was relatively small, using the same cohort of patients for drug regimen comparisons provided some validity for the study. Therefore, the Clinical Pharmacology review team recommends the starting dose of 300 mg Q2W, and patients may consider to taper down to 300 mg Q4W after (b) (4) months.

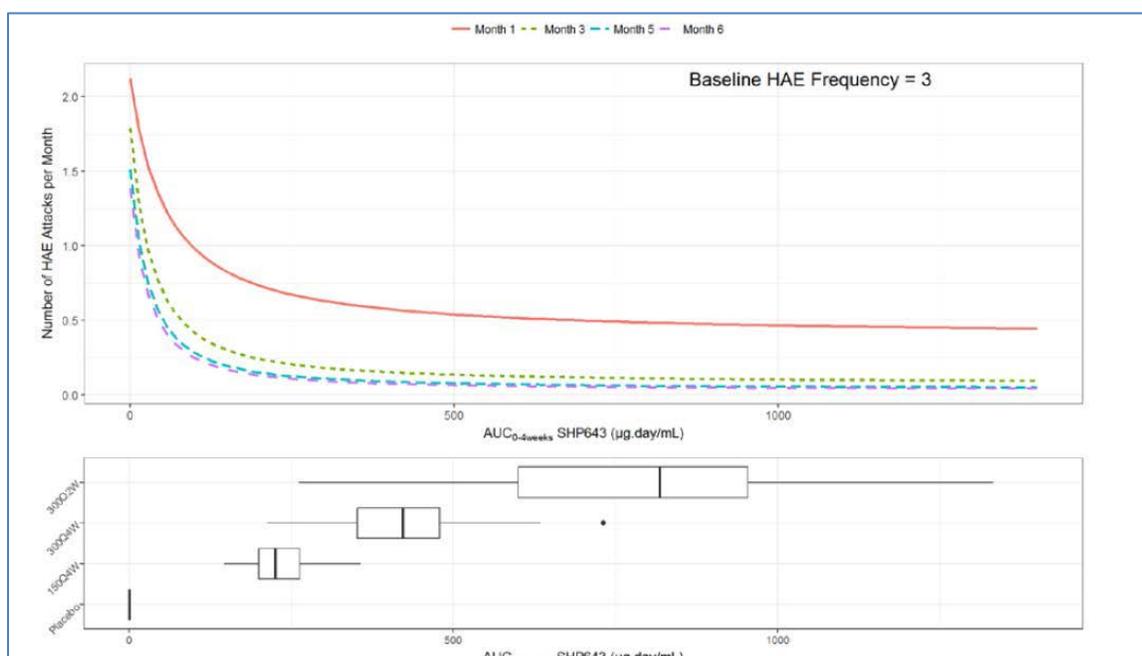
### Exposure-Response for efficacy

An exposure response analysis for efficacy was performed using number of HAE attacks per month and a longitudinal exposure-response model to assess the impact of treatment duration

and drug exposure in Study DX-2930-03 The steepness of the exposure-response function of lanadelumab changed over time, with an apparent plateauing effect at Month 5-6 (Figure 24).

At Month 1, mean  $AUC_{0-4weeks,ss}$  following SC dosing of 150 mg q4w, 300 mg q4w, and 300 mg q2w in study DX-2930-03 were associated with an average HAE attack of 0.583, 0.473, and 0.411, respectively (solid red line, Figure 24). At Month 6, mean  $AUC_{0-4weeks,ss}$  following SC dosing of 150 mg Q4W, 300 mg Q4W, and 300 mg Q2W in study DX-2930-03 were associated with an average HAE attack of 0.105, 0.0673, and 0.0499, respectively (dotted purple line, Figure 24). No further improvement is expected after dosing for 6 months. The exposure response is consistent with the dose response observed in rollover patients in Study DX2930-03 and DX2030-04, where the efficacy is similar for 300 mg q4w and 300 mg q2w after 4 months.

**Figure 24. Exposure-Response Relationship for the Number of HAE Attacks per Month**



Source: Figure 21, summary of clin efficacy

### Dose recommendation

Acknowledging that neither dose-titration nor step-down therapy was formally evaluated in the development program, we have reviewed the data to further explore and understand the dose-response and exposure-response. Though there are limitations to these post-hoc analyses, we believe that there is sufficient data available to support the Q4W interval dosing regimen as an option in labeling. We agree with a recommended starting dose of 300 mg Q2W as this was the most effective dose in study DX2930-03. However, extending the dosing interval beyond Q2W allows flexible dosing for patients and transitioning from every 2 to Q4W after (b) (4) 6 months of dosing does not appear to have an impact on efficacy.

***Safety***

Per the Applicant, most treatment-emergent adverse events (TEAEs) were considered mild and moderate. See section 8 for detailed information on safety assessment. An exploratory exposure-response analysis was performed to assess the relationships between steady state exposure area under the curve to lanadelumab and selected safety endpoints. There is no clear exposure-response relationship for the maximum change from baseline in AST, ALT and bilirubin or maximum change from baseline in aPPT, erythrocyte count, WBC and platelet count.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

Clinical studies DX-2930-03 and DX-2930-04 evaluated the adult and adolescent populations; inclusion of adolescents in these studies was justified based on the similarity of the pathophysiology and clinical presentation of HAE in adults and adolescents, as well as by the lack of any safety signal identified in nonclinical and clinical studies to date. A priori there is no biological reason to suspect that lanadelumab would have any elevated safety risks in adolescents (See section 8.2 for details).

X Jianmeng Chen

Primary Reviewer

X Jingyu Yu

Pharmacometrics Team Leader

X Anshu Marathe

Team Leader

X Chandradas G Sahajwalla

Division Director

(e-signatures located on the last page)

## 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 23. Listing of clinical trials relevant to this BLA**

Trial Identity/ Dates/ClinicalTrials. gov ID#	Trial Design	Regimen (mg)*	Study Endpoints (1° and Key 2°)†	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<b>Controlled Phase 3 Studies to Support Efficacy and Safety</b>							
DX-2930-03 (HELP Study)  3/3/16 – 4/13/17 NCT02586805	R, DB, PC, PG	<ul style="list-style-type: none"> <li>• 150 mg Q4W</li> <li>• 300 mg Q4W</li> <li>• 300 mg Q2W</li> <li>• Placebo Q2W</li> </ul>	# HAE attacks # HAE attacks requiring acute treatment # mod-severe HAE attacks	26 weeks / 8 weeks	159 screened 126 randomized 125 treated 113 completed	≥ 12 years of age with Type I or II HAE	41 sites  US, Germany, Italy, United Kingdom, Canada, Jordan
<b>Uncontrolled Studies to Support Safety</b>							
DX-2930-04 (HELP Study Extension)  5/26/16 – ongoing NCT02741596	OL, single arm	<ul style="list-style-type: none"> <li>• 300 mg Q2W</li> </ul>	Long-term safety Time to first HAE attack in rollover subjects‡	130 weeks / 4 weeks	109 rollover 103 non-rollover	≥ 12 years of age with Type I or II HAE	43 sites  US, Germany, Italy, United Kingdom, Canada, Jordan
<b>Phase 2 Dose-ranging studies</b>							
DX-2930-02  2/14/14 – 5/18/15 NCT02093923	R, DB, PC, MAD	<ul style="list-style-type: none"> <li>• 30 mg Q2W</li> <li>• 100 mg Q2W</li> <li>• 300 mg Q2W</li> <li>• 400 mg Q2W</li> <li>• Placebo Q2W</li> </ul>	Safety, tolerability, PK	2 doses / 120 days	47 screened 38 randomized 37 treated 36 completed	≥ 18 years of age with Type I or II HAE	13 sites  US
DB=double-blind, HAE=hereditary angioedema, MAD=multiple ascending dose, OLE=open label extension, PC=placebo-controlled, PG=parallel group, PK=pharmacokinetic, Q2W=every 2 weeks, Q4W=every 4 weeks, R=randomized, *All doses administered subcutaneously †investigator-confirmed HAE attacks during the treatment period (Days 0-182) in study DX-2930-03 ‡ Time from first open label dose							

## 7.2. Review Strategy

Support for the efficacy and safety of lanadelumab in the proposed indication is primarily based on a single, 26-week multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in 125 adult and adolescent patients with Type I or II HAE, Trial DX-2930-03. Efficacy results from Trial DX-2930-03 are presented in Section 8.1.1.1. FDA biostatistician, Susan Duke, MS confirmed the Applicant's efficacy analyses and generated tables and figures for this review. For the evaluation of safety, FDA medical officer Dr. Stacy Chin analyzed data from Trial DX-2930-03 as well as from open label extension (OLE) study DX-2930-04 using JMP, JMP Clinical, JReview, MAED, and Demographic Tool in the OCS Analysis Toolbox. The safety results presented in Section 8.2 represent the medical officer reviewer's own analyses. For brevity, trials/studies may also be referred to in this review by the last 2 digits of the study name.

## 8 Clinical and Statistical Evaluation

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### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

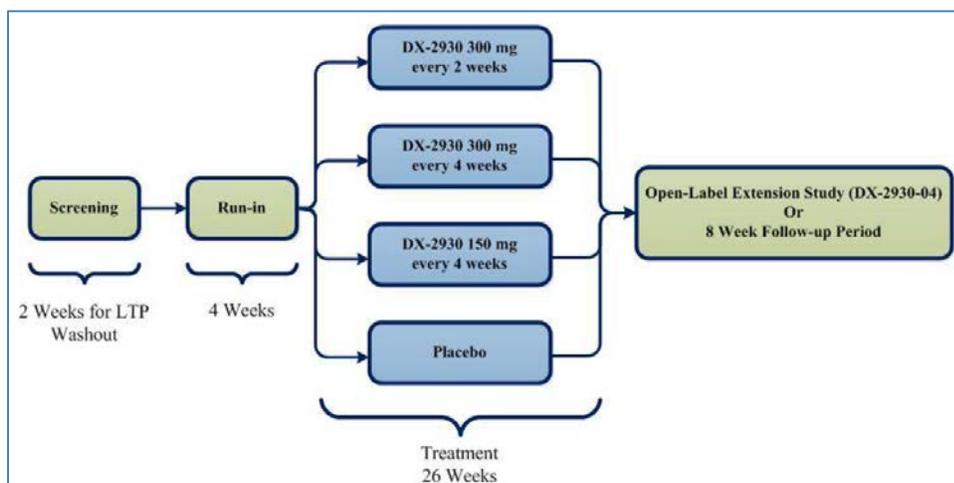
#### 8.1.1. DX-2930-03 (HELP Study)

##### Trial Design

This was a 26-week, multicenter, randomized, double-blind, placebo-controlled, parallel group trial evaluating the efficacy and safety of three dose/dosing regimens of lanadelumab for the prevention of acute attacks in adolescent and adult patients with Type I and Type II HAE. Following informed consent, subjects aged 18 years and older underwent a minimum 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. (Subjects not currently taking long term prophylaxis did not require the 2-week washout period.) Following screening, subjects entered a 4-week run-in period to determine the baseline HAE attack rate. Subjects meeting a minimum baseline rate of at least one investigator-confirmed HAE attack (per 4 weeks) during run-in were eligible for enrollment. Subjects not meeting the minimum attack rate during the first 4 weeks were allowed to extend the run-in period for another 4 weeks (8 weeks total). Subjects experiencing three or more attacks during the run-in period were allowed to exit the run-in period early. Eligible subjects were randomized 2:1 to receive lanadelumab or placebo with active treatment arms randomized equally to one of three dose regimens. The treatment period consisted of 13 doses of study drug over 26 weeks; study visits occurred every 2 weeks. Following treatment, subjects entered an 8-week follow up period or rolled over into an open label extension (OLE) study, DX-2930-04. A schematic of the study design and table of study assessments are shown below in Figure 25 and Figure 26.

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Figure 25. Study design schematic: DX-2930-03



Source: DX-2930-03 protocol, Figure 1, p40

Figure 26. Schedule of study assessments: DX-2930-03

	Study Activities Schedule															
	Screening Visit	Run-in Period <sup>1</sup>	Treatment Period <sup>2</sup>													Follow-up Period <sup>3</sup>
Tests and Assessments		Visit 1 Dose 1 Day 0	Site Check-in <sup>4</sup>	Visit 2 Dose 2 Day 14	Visit 3 Dose 3 Day 28	Visit 4 Dose 4 Day 42	Visit 5 Dose 5 Day 56	Visits 6 and 7 Doses 6 and 7 Days 70 and 84	Visit 8 Dose 8 Day 98	Visits 9 and 10 Doses 9 and 10 Days 112 and 126	Visit 11 Dose 11 Day 140	Day 144±1	Visits 12 and 13 Doses 12 and 13 Days 154 and 168	Visit 14 Day 182	Visit 15 Day 210	Visit 16 Day 238
Informed Consent	X															
Eligibility Review	X	X														
Long-term Prophylactic Therapy Washout <sup>5</sup>	X															
Randomization		X														
Blinded IMP Treatment		X		X	X	X	X	X	X	X	X		X			
Demographic and Medical History	X															
CI-DNH, C1q and C4 Testing <sup>6</sup>	X															
Pregnancy Test <sup>7</sup> (females)	X	X		X		X		X	X	X			X	X		X
Vital Signs <sup>8</sup>	X	X		X	X	X	X	X	X	X	X		X	X	X	X
Physical Examination <sup>9</sup>	X	X		X		X		X		X				X		X
12-Lead ECG <sup>10</sup>	X	X					X					X		X		X
Clinical Laboratory Testing <sup>11</sup>	X	X		X		X		X		X		X		X		X
Serologies: HBsAg, HCV, and HIV	X															
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
HAE Attack Data <sup>12</sup>	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Quality of Life Assessments <sup>13</sup>		X		X		X		X	X	X			X	X		X
PK Blood Sampling		X				X		X		X				X	X	X
PD Sample Collection		X				X		X		X				X	X	X
Plasma Anti-Drug Antibody Testing		X				X		X		X				X		X
Discharge from Study <sup>14,15</sup>														X		X

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## Takhzyro (Ivanadelumab)

BP = blood Pressure; C1-INH = C1 Inhibitor; C<sub>max</sub> = Maximum plasma drug concentration; ECG = Electrocardiogram; HAE = hereditary Angioedema; HbsAg = Hepatitis B Surface Antigen; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency virus; HR = Heart Rate; IMP = Investigational Medicinal Product; LTP = Long-term Prophylactic; OLe = Open-label Extension; PD = Pharmacodynamic; PK = Pharmacokinetic; RR = Resting Rate

1. Subjects will undergo a run-in period to determine their baseline HAE attack rate. Only subjects with a baseline rate of at least 1 Investigator-confirmed HAE attack per 4 weeks will be eligible for enrollment and randomization. Subjects who experience 3 or more Investigator-confirmed attacks before the end of the 4 weeks can exit the run-in period early and proceed to enrollment and randomization. Subjects without at least 1 Investigator-confirmed attack after 4 weeks of run-in will have their run-in period extended for another 4 weeks, during which time they need to have at least 2 Investigator-confirmed attacks to proceed to enrollment and randomization. To be eligible for enrollment, subjects who have their run-in extended must complete the full 8-week run-in period prior to entering the treatment period. Subjects who do not meet the minimum attack rate during run-in or are otherwise determined to be ineligible due to screening assessments will be considered a screen fail.
2. Treatment Period visits have a ±3 day window, with a maximum of 17 days or a minimum of 11 days between any two doses, starting with Dose 2, Day 14 through Day 182.
3. For subjects who do not rollover into OLe (DX-2930-04), Follow-up visits have a ±3 day window.
4. Site personnel contact the subject to solicit for any attacks not already reported by the subject once between scheduled site visits or approximately 7 days after last contact with subject.
5. Subjects who are on long-term prophylactic (LTP) therapy for HAE are required to undergo a minimum 2 week washout period prior to the start of the run-in period. This LTP washout is permitted as long as the Investigator determines that doing so would not place the subject at any undue safety risk and the subject is at least 18 years of age. The Investigator must confirm that the subject has successfully completed the 2 week washout period before they can enter the run-in period.
6. Samples for C1-INH, C4, and C1q assays will be obtained at screening for eligibility assessment.
7. The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 and Day 182 must be urine-based. Tests performed at screening, Days 28, 56, 98, 126, 154, and Day 238 can be serum- or urine-based.
8. There is a 15 minute window for all vital signs. At study visits in which IMP is administered, vital signs including sitting or supine BP, HR, body temperature, and RR, will be obtained prior to dosing, 1 hour after dosing, and 2 hours after dosing for the first 4 doses with the ability to eliminate the 2 hour vitals for the remaining doses based on the discretion of the Investigator and the absence of safety signals.
9. Height and weight will be collected at the Screening visit only.
10. ECGs (single recordings) are collected at screening, baseline prior to Dose 1, Day 56, Day 144±1 day to capture the estimated C<sub>max</sub> and Day 182. The ECG assessment at C<sub>max</sub> on Day 144±1 day may be performed via at-home nurse or technician in lieu of a subject visit to the study site.
11. Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis.
12. Historical attack information will be collected at screening. During the study subjects (or caregivers, in the event the subject is < 18 years old or is incapacitated) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. Site personnel will also contact the subject once a week or at approximately 7 days after last contact with the subject during the run-in period and once between study visits or approximately 7 days after last contact with the subject during the treatment period in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not given through prior subject contact with the site.
13. Quality of life data will be obtained using the EuroQoL Group 5-Dimension (EQ5D) Self-Report Questionnaire at pre-dose on Days 0, 98±3, and 182±3 and using the Angioedema Quality of Life Questionnaire (AE-QoL) at pre-dose on Days 0, 28±3, 56±3, 98±3, 126±3, 154±3, and 182±3. An additional quality of life assessment (EQ5D and AE-QoL) will be conducted on Day 238±3 for subjects not entering OLe.
14. Subjects who rollover into the Open-Label Extension protocol (DX-2930-04) will provide consent by Day 182 and receive their first open-label dose following the completion of all DX-2930-03 assessments scheduled on Day 182. At the completion of these assessments, the subject will be discharged from DX-2930-03 and roll into the DX-2930-04 study.
15. Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures as Day 182 at their final study visit.

Source: DX-2930-03 protocol, Table 1, p19

### *Trial population*

The study population included adults and adolescents (12 to 17 years of age) with a confirmed diagnosis of Type I or II HAE and a minimum baseline attack rate of 1 investigator-confirmed attack per 4 weeks (month) during the run-in period. Subjects were stratified by baseline attack rate: 1 to < 2 attacks/month, 2 to <3 attacks/month, and ≥3 attacks/month.

### Key inclusion criteria

1. Males and females 12 years of age or older at screening
2. Type I or II HAE based on:
  - a. Documented clinical history consistent with HAE and
  - b. C1-INH function level <40% of normal or C1-INH level 40-50% of normal with low C4 and
  - c. Age at symptom onset ≤30 years, family history consistent with Type I/II HAE, or normal C1q
3. At least 1 investigator-confirmed HAE attack per 4 weeks during run-in

### Key exclusion criteria

1. Diagnosis of another form of chronic angioedema (e.g., acquired angioedema, Type III HAE, idiopathic angioedema, chronic angioedema with urticaria)
2. Participation in prior DX-2930 (Ivanadelumab) study
3. ACE inhibitor or estrogen containing medication within 4 weeks prior to screening
4. Long-term HAE prophylaxis (e.g., C1-INH, androgens, anti-fibrinolytics) within 2 weeks prior to run-in
5. Short-term HAE prophylaxis within 7 days prior to run-in, defined as C1-INH, attenuated

androgens, or anti-fibrinolytics to avoid angioedema complications from medically indicated procedures

6. Liver function test abnormalities: ALT or AST >3x ULN or total bilirubin >2x ULN (except for bilirubin elevation due to Gilbert's syndrome)
7. Pregnancy or breastfeeding

*Subject removal criteria*

Individual subjects were discontinued for drug-related SAEs or clinically significant AEs at the Investigator's discretion. Subjects who prematurely discontinued study treatment were followed for the duration of the 26-week treatment period, unless they requested to be discontinued from the study. Premature discontinuations were not eligible to participate in the OLE.

*Study treatments and blinding*

Lanadelumab 150 mg SC every 4 weeks (1 mL injection of lanadelumab and 1 mL injection of placebo)

Lanadelumab 300 mg SC every 4 weeks (two 1 mL injections of lanadelumab)

Lanadelumab 300 mg SC every 2 weeks (two 1 mL injections of lanadelumab)

Placebo SC every 2 weeks (two 1 mL injections of matching placebo)

All study drug was blinded to both subjects and study staff. All doses were administered during study visits subcutaneously in the upper arm with at least 2 cm between injection sites. To maintain the blind, subjects randomized to lanadelumab 150 mg or 300 mg Q4W received placebo injections at every other study visit as shown in Figure 27.

**Figure 27. Dosing schedule: DX-2930-03**

Dose Number	Treatment Period Dose Day/Week	Treatment Arms: DX-2930 or Placebo			
		300 mg every 2 weeks	300 mg every 4 weeks	150 mg every 4 weeks	Placebo
1	Day 0/Week 0	DX-2930	DX-2930	DX-2930	Placebo
2	Day 14/Week 2	DX-2930	Placebo	Placebo	Placebo
3	Day 28/Week 4	DX-2930	DX-2930	DX-2930	Placebo
4	Day 42/Week 6	DX-2930	Placebo	Placebo	Placebo
5	Day 56/Week 8	DX-2930	DX-2930	DX-2930	Placebo
6	Day 70/Week 10	DX-2930	Placebo	Placebo	Placebo
7	Day 84/Week 12	DX-2930	DX-2930	DX-2930	Placebo
8	Day 98/Week 14	DX-2930	Placebo	Placebo	Placebo
9	Day 112/Week 16	DX-2930	DX-2930	DX-2930	Placebo
10	Day 126/Week 18	DX-2930	Placebo	Placebo	Placebo
11	Day 140/Week 20	DX-2930	DX-2930	DX-2930	Placebo
12	Day 154/Week 22	DX-2930	Placebo	Placebo	Placebo
13	Day 168/Week 24	DX-2930	DX-2930	DX-2930	Placebo
--	Day 182/Week 26	No Dose	No Dose	No Dose	No Dose

Source: DX-2930-03 protocol, Table 2, p39

### *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 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

### **Study Endpoints**

#### *Primary efficacy endpoint*

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

*Reviewer note: During the study, all HAE attacks were initially captured as AEs. For 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 efficacy endpoints*

- Number of investigator-confirmed HAE attacks requiring acute treatment (Day 0 through 182)
- Number of moderate or severe investigator-confirmed HAE attacks (Day 0 through 182)
- Number of investigator-confirmed HAE attacks (Day 14 through 182)

#### *Exploratory efficacy endpoints*

- Time to first HAE attack after Day 14
- Number of high morbidity investigator-confirmed HAE attacks (i.e., severe, requires hospitalization, hemodynamically significant, or laryngeal)

### HAE attacks

Defined as an event with signs or symptoms consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region
- Abdominal angioedema: abdominal pain, with or without abdominal distension, nausea, vomiting, or diarrhea
- Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx

The investigator may have determined that the event did not represent an HAE attack, despite presence of the above symptoms, if there were atypical features strongly suggestive of an

alternative diagnosis. Prodromal symptoms by themselves were not considered an attack. Use of acute HAE attack treatment alone was not considered an attack.

Unique attacks must have been separated by at least 24 hours. Attack resolution was defined as the absence of attack symptoms.

During the trial, subjects or caregivers were instructed to contact the study site within 72 hours of the start of attack symptoms. Study staff solicited additional information as necessary to document the attack. Study staff contacted subjects/caregivers at pre-specified intervals to solicit for any attacks that may have occurred but were not reported. The investigator reviewed attack information to confirm if the event represented an HAE attack.

The following information was collected for each attack report:

- Date/time of symptom onset
- Description of symptoms, including location
- Impact on activity level
- Need for assistance, medical intervention, emergency room visit, or hospitalization
- Medications to treat the attack
- Date/time symptoms resolved

Additional probing questions included:

- If only prodromal symptoms were experienced
- Difference from typical HAE attacks
- Possible alternative etiologies (ex: viral gastroenteritis)

The site determined the overall severity of the subject's attack using the following definitions:

- Mild: transient or mild discomfort
- Moderate: mild to moderate limitation in activity, some assistance needed
- Severe: marked limitation in activity, assistance required

### *Safety assessments*

Safety monitoring included recording of treatment emergent adverse events (TEAEs), physical exams, vital signs (temperature, HR, BP, RR), clinical laboratory tests (hematology, chemistry, LFTs, coagulation, urinalysis, pregnancy), 12-lead ECG, and anti-drug antibodies (ADA) according to the schedule in Figure 26.

### *Quality of life assessments*

Quality of life data was obtained using the EuroQoL Group 5-Dimension (EQ5D) Questionnaire at pre-dose on Days 0, 98, and 182 and using the Angioedema Quality of Life (AE-QoL) Questionnaire at pre-dose on Days 0, 28, 56, 98, 126, 154, and 182. An additional assessment was conducted on Day 238 for subjects not rolling over into the OLE.

### Statistical Analysis Plan

The applicant states that this statistical analysis plan (SAP) was developed after the protocol, but before database lock and unblinding of treatment assignment. It contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the clinical study report (CSR). This SAP was written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline, entitled Guidance for Industry: Statistical Principles for Clinical Trials, and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

The SAP describes the analysis sets used for analysis, as well as subject characteristics, efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PD), and quality of life (QoL) parameters. Details were provided of the specific statistical methods as stated in the protocol and any changes from the protocol-specified analyses were documented in the SAP prior to database lock.

The analysis populations were defined as follows:

1. Intent-to-treat (ITT) population included all randomized subjects who received any exposure to the investigational product.
2. Safety population included all subjects who received any exposure to the investigational product.

The primary efficacy analyses were performed using the ITT population. For efficacy analyses, subjects were analyzed per their randomized treatment assignment regardless of the treatment received.

The individual stopping rules as defined in the protocol were for patients discontinuing study drug to continue the study through completion of all scheduled visits. The SAP description of time to first HAE attack analysis does not distinguish between treatment discontinuation and study discontinuation. Data collected from patients who discontinued study drug but remained in the study were apparently not included in this or other analyses. Use of the patient's own data post study drug discontinuation provides the HCP and patient a treatment policy estimand, giving more analytic clarity on what patients who take a drug experience not only when it is working, but also incorporates their experience when they need to discontinue drug.

The primary efficacy endpoint, number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182), was compared for each active treatment group (DX-2930) to the placebo group using a generalized linear model (GLM) for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential over dispersion. The model includes fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the

logarithm of time in days each subject was observed during the treatment period was used as an offset variable in the model.

From this model, the least squares mean rate and standard error for each treatment group as well as the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals for each active treatment group were estimated. These estimates were reported as mean event rates per unit of time (week and monthly) by transforming the estimates using the exponential function and scaling by the unit of time.

The primary endpoint was tested by the following hypothesis:

$$H_0: \lambda_{\text{DX-2930}} / \lambda_{\text{placebo}} = 1 \text{ versus } H_1: \lambda_{\text{DX-2930}} / \lambda_{\text{placebo}} \neq 1$$

$\lambda_{\text{DX-2930}}$  refers to the mean investigator-confirmed HAE attack rate in the DX-2930 group and  $\lambda_{\text{placebo}}$  refers to the mean investigator-confirmed HAE attack rate in the placebo group. The null hypothesis is that the mean investigator-confirmed HAE attack rate ratio is 1 (no difference between treatment groups), versus the alternative hypothesis that the HAE attack rate ratio is not 1. Estimated attack rate ratios less than one would indicate that subjects treated with DX-2930, on average, have a lower incidence of investigator-confirmed HAE attacks during the treatment period. The hypothesis was tested using the model-based least squares means estimate of the treatment difference using a Wald-based chi-square test.

The percentage difference in mean investigator-confirmed HAE attack rate of each active treatment group from the attack rate of placebo was calculated as  $100\% * (\text{mean rate ratio} - 1)$ . Similarly, the estimated upper and lower confidence limits for the mean rate ratio could be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change. The mean rate ratios and corresponding 95% confidence intervals will be estimated from the generalized linear model as described previously.

To maintain the overall Type I error at two-sided 0.05, a conservative Bonferroni-based procedure was used for the comparisons of each of the active treatment groups with the placebo group with equal weights for each test, resulting in a 0.0167 significance level (0.05/3) for each test.

Formal statistical hypothesis testing was performed on the primary and rank ordered secondary efficacy endpoints with the global family-wise type I error rate (FWER) strongly controlled for multiplicity at two-sided 0.05 using a Bonferroni-based general gatekeeping procedure. Branches for each active treatment group to placebo group comparison were utilized where statistical tests were conducted in a sequential manner at the 0.0167 level.

The rank ordered secondary efficacy endpoints were as follows:

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

3. Number of Investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182 (Day 14 through Day 182)

The secondary endpoints were analyzed using the same method as described for the primary efficacy endpoint.

The Applicant conducted several planned sensitivity analyses on the primary efficacy endpoint and/or secondary endpoints to evaluate the robustness of the results. Tipping point analysis using the multiple imputation method was conducted to measure the potential effect of missing data on the reliability of efficacy results. Using the multiple imputation approach, subjects who did not complete the treatment period, with the early discontinuation day prior to Day 182, had their HAE attack data for the missing part of the study randomly imputed using the primary analysis model and an assumption that events occur with the same underlying rate within an individual as was observed prior to dropout. Next, a multiplication factor with progressively more conservative assumptions, i.e., higher post-dropout attack rates, was applied to subjects treated with lanadelumab. Then the plausibility of the tipping point, i.e., the multiplication factor resulting in no significance, was to be evaluated. A sensitivity analysis using the negative binomial GLM in comparison to the primary Poisson GLM to analyze the number of attacks was also conducted to assess whether the corrections for overdispersion were consistent between the two methods.

Ad hoc analyses were conducted to analyze the time to first attack after Day 0 (after 1 dose) and after Day 28 when subjects would have had either 2 lanadelumab doses (Q4W) or 3 doses (Q2W). An ad hoc analysis was also conducted to analyze the time to first attack after Day 70 (when lanadelumab concentration appeared to reach steady state).

All safety analyses were performed using the safety population. Subjects were analyzed per the treatment received regardless of treatment assignment.

### **Protocol Amendments**

The Applicant amended the protocol three times with the following key changes:

#### *Amendment 1 (December 14, 2015)*

- Clarified the requirements for extended run-in periods (subjects must complete full 8 week run-in)
- Specified target enrollment for adolescent subjects (n=5)
- Clarified investigator role in discontinuing subject dosing and breaking the blind
- Updated concentration of lanadelumab from 100 mg/mL to 150 mg/mL based on manufacture changes

#### *Amendment 2 (April 21, 2016)*

- Excluded subjects who participated in prior DX-2930 studies (per FDA recommendation);

- consequently, stratification by naïve vs non-naïve was removed
- Efficacy evaluation period updated from Day 14 through 182 to Day 0 through 182 (per FDA recommendation)
  - Time to first HAE attack and number of high-morbidity HAE attacks moved from secondary to exploratory efficacy endpoints
  - Updated statistical methods for the primary and secondary efficacy endpoints from a generalized estimating equation model to a generalized linear model
  - Multiplicity procedures were specified in greater detail
  - Sample size determination was updated to be consistent with the updated statistical methods
  - Added more AE-QoL Questionnaire assessment timepoints
  - Clarified that no interim analysis is planned
  - Replaced the internal study safety committee with an independent data safety monitoring board (DSMB)
  - Added more pregnancy test assessment timepoints

*Amendment 3 (January 09, 2017)*

- Added an efficacy measure to assess the number of investigator-confirmed HAE attacks on Days 14 through 182 to the secondary endpoints for inclusion in the multiple testing procedure (third in rank order)
- Updated the multiplicity procedure by adding the “Family 4 (F4)” hypothesis test to the 3-branch general gatekeeping procedure for the third ranked secondary efficacy endpoint

### **8.1.1.1. DX2930-03 Study Results**

#### **Compliance with Good Clinical Practices**

The Applicant states that the study was conducted in accordance with GCP as described in ICH guidelines. The study protocol, amendments, informed consent, and other necessary documents were reviewed and approved by an independent ethics committee (IEC) or institutional review board (IRB) before initiation of the study. Written informed consent and assent, where applicable, was obtained from each subject before study participation. This study was conducted under IND 116,647.

#### **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)

#### **Patient Disposition**

Screen failures were most often due to normal C1-INH and/or C4 labs and insufficient number

of baseline HAE attacks during run-in. One placebo subject was prematurely discontinued from treatment based on physician discretion because of noncompliance and missed study visits (Table 24). Withdrawals by subject included:

- 1 placebo subject felt she was receiving placebo
- 5 subjects no longer wanted to be in the study due to personal reasons (e.g., not enough time, moved out of state) or other medical reasons
- 1 subject (lanadelumab 300 Q2W) withdrew following a serious laryngeal HAE attack and has been re-categorized under “adverse event” as reason for withdrawal in the table below

**Table 24. Subject disposition: DX-2930-03**

	Placebo	LAN 150 Q4W	LAN 300 Q4W	LAN 300 Q2W	Total
Screened					159
Randomized	41	29	29	27	126
Treated (Safety Population)	41	28	29	27	125
Intent-To-Treat (ITT Population)	41 (100)	28 (100)	29 (100)	27 (100)	125 (100)
Completed Treatment	35 (85)	27 (93)	26 (90)	25 (93)	113 (90)
Rollover to OLE	33 (81)	26 (90)	25 (86)	25 (93)	109 (87)
Prematurely discontinued treatment	6 (15)	1 (4)	3 (10)	2 (7)	12 (10)
Adverse event*	2 (5)	0	1 (3)	1 (4)	4 (3)
Lost to follow up	0	0	1 (3)	0	1 (1)
Physician decision	1 (2)	0	0	0	1 (1)
Withdrawal by subject*	3 (7)	1 (4)	1 (3)	1 (4)	6 (5)

LAN=lanadelumab, Q4=every 4 weeks, Q2=every 2 weeks  
Source: Reviewer generated table in JMP Clinical using ADSL and DS datasets.  
\*one withdrawal by subject in the lanadelumab 300 Q2W group re-categorized as adverse event

Subjects in the Safety and ITT Populations were the same. One additional subject was randomized to the 150mg Q4W arm but was determined to be a screen failure prior to receiving any study medication.

### Protocol Violations/Deviations

Two subjects (both lanadelumab 300 Q4W) self-administered prohibited HAE prophylactic medications: one subject used Firazyr off-label for prophylaxis and one subject used 6000 units of Berinert for a flare of rheumatoid arthritis. Neither protocol violation appears to have continued for a prolonged period of time and thus neither are likely to impact the efficacy results. Numerous other minor protocol deviations occurred related to the timing of study visits, lab, questionnaire, and ECG assessments, and reporting of HAE attacks (i.e., failure to contact study site to report attack within 72 hours of symptom onset).

### Table of Demographic Characteristics

Subject demographic characteristics are shown in Table 25 and were generally similar across treatment arms for a small study. Overall, the study enrolled more females than males. The

proportion of females was higher in the placebo arm (83%) than in the active lanadelumab arms (56-71%). Representation in the youngest (12-17 years) and oldest ( $\geq 65$  years) age groups was relatively low. A minority of subjects (10% across treatment arms) were non-white, varying from 4% (300mg Q2W arm) to 21% (300mg Q4W arm). Most subjects were from the United States (69%) and Europe (23%), with the remaining 6% from Canada and 2% from Jordan.

*Reviewer Comments: While HAE affects males and females equally, the literature reports a clear female predominance, most likely because women tend to be more symptomatic than men owing to hormonal factors such as puberty, contraception, and pregnancy.<sup>31, 32</sup> Thus, the predominantly female study population is not concerning and merely a reflection of the most symptomatic patients who are most likely to use and benefit from prophylactic treatment. 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. The representation of non-white patients in this study, while relatively low, is adequate for such a rare disease. The pathophysiology of the disease is the same regardless of age, therefore, the proportion of adolescent subjects in this study is also sufficient.*

**Table 25. Demographic characteristics of the ITT population: DX-2930-03**

Demographic Parameters	Placebo (N=41) n (%)	Lanadelumab Treatment Groups (N=84)			Total (N= 125) n (%)
		LAN 150 Q4 (N=28) n (%)	LAN 300 Q4 (N=29) n (%)	LAN 300 Q2 (N=27) n (%)	
<b>Sex</b>					
Male	7 (17)	8 (29)	10 (35)	12 (44)	37 (30)
Female	34 (83)	20 (71)	19 (66)	15 (56)	88 (70)
<b>Age</b>					
Mean years (SD)	40 (17)	43 (15)	39 (13)	40 (13)	40 (15)
Median (years)	42	45	40	38	42
Min, max (years)	12, 70	15, 73	12, 59	15, 61	12, 73
<b>Age Group</b>					
< 18 years	4 (10)	1 (4)	3 (10)	2 (7)	10 (8)
$\geq 18$ to <65 years	35 (85)	24 (86)	26 (90)	25 (93)	110 (88)
$\geq 65$ years	2 (5)	3 (11)	0	0	5 (4)
<b>Race</b>					
White	39 (95)	25 (89)	23 (79)	26 (96)	113 (94)
Black or African	2 (5)	1 (4)	6 (21)	1 (4)	10 (8)

<sup>31</sup> Agostoni A, Cicardi M. Hereditary and acquired C1 inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine*. 1992;71:206–215

<sup>32</sup> Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs and course. *Am J Med*. 2006;119:26–274

Demographic Parameters	Placebo (N=41) n (%)	Lanadelumab Treatment Groups (N=84)			Total (N= 125) n (%)
		LAN 150 Q4 (N=28) n (%)	LAN 300 Q4 (N=29) n (%)	LAN 300 Q2 (N=27) n (%)	
American					
Asian	0	2 (7)	0	0	2 (2)
<b>Ethnicity</b>					
Hispanic or Latino	3 (7)	1 (4)	2 (7)	3 (11)	9 (7)
Not Hispanic or Latino	38 (93)	27 (96)	38 (93)	23 (85)	115 (92)
Unknown	0	0	0	1 (4)	1 (1)
<b>Region</b>					
United States	25 (61)	20 (71)	23 (79)	18 (67)	86 (69)
Rest of the World					
Canada	3 (7)	1 (4)	1 (3)	2 (7)	7 (6)
Europe	12 (29)	6 (21)	4 (14)	7 (26)	29 (23)
Jordan	1 (2)	1 (4)	1 (3)	0	3 (2)

Source: Reviewer generated table in JMP clinical using ADSL dataset

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Baseline disease characteristics were generally similar across treatment arms (Table 26). Most patients have Type I HAE, which reflects the reported epidemiology. The proportion of subjects on prior long-term prophylactic treatment ranged from roughly 40-60%, the majority of which was C1-INH replacement therapy. The placebo and 300mg Q4W arms had a larger proportion of subjects on prior prophylactic treatment (54% and 62% respectively) compared to the 150mg Q4W and 300mg Q2W arms (32% and 41% respectively), indicating that these groups may have consisted of patients with more severe disease. The baseline attack rate during the run-in period was similar among treatment groups with roughly half of patients experiencing three or more attacks per month (defined as 4 weeks). Approximately one-quarter of patients reported laryngeal involvement as a primary attack location and nearly two-thirds reported a history of laryngeal attacks in the past. Overall, the study population was representative of an HAE patient population for whom long-term prophylaxis with a mAb would be appropriate.

**Table 26. Baseline characteristics of ITT population: DX-2930-03**

Baseline Characteristics	Placebo (N=41) n (%)	Lanadelumab Treatment Groups (N=84)			Total (N= 125) n (%)
		LAN 150 Q4W (N=28) n (%)	LAN 300 Q4W (N=29) n (%)	LAN 300 Q2W (N=27) n (%)	
<b>Weight (kg)</b>					
Mean (SD)	76 (23)	78 (16)	79 (17)	91 (25)	80 (21)
Median	70	77	76	87	76
Min, max	37, 146	50, 116	47, 121	55, 150	37, 150

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Baseline Characteristics	Placebo (N=41) n (%)	Lanadelumab Treatment Groups (N=84)			Total (N= 125) n (%)
		LAN 150 Q4W (N=28) n (%)	LAN 300 Q4W (N=29) n (%)	LAN 300 Q2W (N=27) n (%)	
<b>BMI (kg/m<sup>2</sup>)</b>					
Mean (SD)	28 (8)	27 (5)	28 (5)	31 (8)	28 (7)
Median	27	26	27	28	27
Min, max	17, 55	19, 39	18, 38	21, 48	17, 55
<b>Weight Group (kg)</b>					
<50	2 (5)	0	1 (3)	0	3 (2)
50 to <75	24 (59)	12 (43)	13 (45)	10 (37)	59 (47)
75 to <100	9 (22)	14 (50)	11 (38)	8 (30)	42 (34)
≥100	6 (15)	2 (7)	4 (14)	9 (33)	21 (17)
<b>HAE Type</b>					
Type I	38 (93)	25 (89)	27 (93)	23 (85)	113 (90)
Type II	3 (7)	3 (11)	2 (7)	4 (15)	12 (10)
<b>Age at Onset (years)</b>					
Mean (SD)	11 (8)	12 (9)	15 (11)	15 (9)	13 (9)
Median	8	11	12	14	12
Min, max	2, 41	1, 40	1, 49	2, 43	1, 49
<b>Baseline HAE Attack Rate/Month</b>					
Mean (SD)	4 (3)	3 (2)	4 (3)	4 (2)	4 (3)
Median	3	3	3	3	3
Min, max	1, 15	1, 7	1, 11	1, 9	1, 15
<b>Baseline HAE Attack Rate Group</b>					
1 to <2 attacks/month	12 (29)	10 (36)	9 (31)	7 (26)	38 (30)
2 to <3 attacks/month	8 (20)	3 (11)	5 (17)	6 (22)	22 (18)
≥3 attacks/month	21 (51)	15 (54)	15 (52)	14 (52)	65 (52)
<b>Primary HAE Attack Location</b>					
Abdominal	11 (27)	3 (11)	7 (24)	3 (11)	24 (19)
Abdominal/Peripheral	15 (37)	14 (50)	14 (48)	14 (52)	57 (46)
Laryngeal/Abdominal	0	0	0	1 (4)	1 (1)
Laryngeal/Abdominal/Peripheral	9 (22)	3 (11)	6 (21)	3 (11)	21 (17)
Laryngeal/Peripheral	1 (2)	0	0	1 (4)	2 (2)
Peripheral	5 (12)	8 (29)	2 (7)	5 (19)	20 (16)
<b>History of laryngeal attacks</b>	27 (66)	17 (61)	17 (59)	20 (74)	81 (65)
<b>Prior LPT therapy</b>					
C1-INH only	22 (54)	9 (32)	18 (62)	11 (41)	60 (48)
Androgens only	1 (2)	2 (7)	0	0	3 (2)
Anti-fibrinolytics only	0	0	1 (3)	0	1 (1)
Androgens and C1-INH	1 (2)	1 (4)	1 (3)	2 (7)	5 (4)
Androgens, Anti-fibrinolytics, and C1-INH	0	0	0	1 (4)	1 (1)
None	17 (41)	16 (57)	9 (31)	13 (48)	55 (44)

Source: Reviewer generated table in JMP clinical using ADSL dataset  
LPT=long term prophylaxis

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Because study drug was administered at the study site, treatment compliance was high. Except for subjects who prematurely discontinued treatment, nearly all subjects received all 13 doses of study drug with only 2-3 subjects each in the placebo, lanadelumab 300 Q2W and 300 Q4W groups receiving 12 doses instead of 13.

### **Efficacy Results**

The study was powered to detect a 60% reduction in HAE attacks, a conservative estimate well below the expected reduction in attacks from the DX-2930-02 study data of close to 100%. Treatment to placebo ratio in sample size was 1:1.5; 24 actively treated subjects and 36 placebo subjects provide at least 95% power ( $\alpha = 0.025$ , one-sided), stratified by baseline attack rate (1 to <2, 2 to <3, and  $\geq 3$  q 4wks). Based on these calculations, the planned enrollment was 80 subjects on the 3 active arms and 40 subjects on placebo treatment. The actual enrollment exceeded the planned enrollment and was adequately powered: 84 subjects on the active arms and 41 subjects on placebo treatment.

### **Primary and Secondary Efficacy Results**

Results for all primary and secondary analysis comparisons, adjusted for multiplicity, were clinically and inferentially strong and consistent relative to placebo across treatment arms. Results for the primary and key secondary endpoints are shown in Figure 28 and Table 27. There was strong evidence ( $p < 0.001$ ) that all three doses of lanadelumab reduce the HAE attack rate relative to placebo. The mean number of HAE attacks per month on placebo was 2.0, as compared to 0.5, 0.5, and 0.3 on lanadelumab 150 mg Q4W, 300 mg Q4W, and 300 mg Q2W, respectively.

Results of the primary analysis were expressed as a rate ratio, which can also be expressed as percent change from placebo (mathematically interchangeable).

There was also evidence of a beneficial effect of all three doses of lanadelumab on the secondary endpoints, number of HAE attacks requiring acute treatment and number of moderate or severe HAE attacks (Figure 28 and Table 27).

**Figure 28. DX-2930-03 Primary Efficacy Results: Poisson regression of HAE Attack rate ratio during treatment (Day 0-182): DX-2930-03 (ITT Population)**

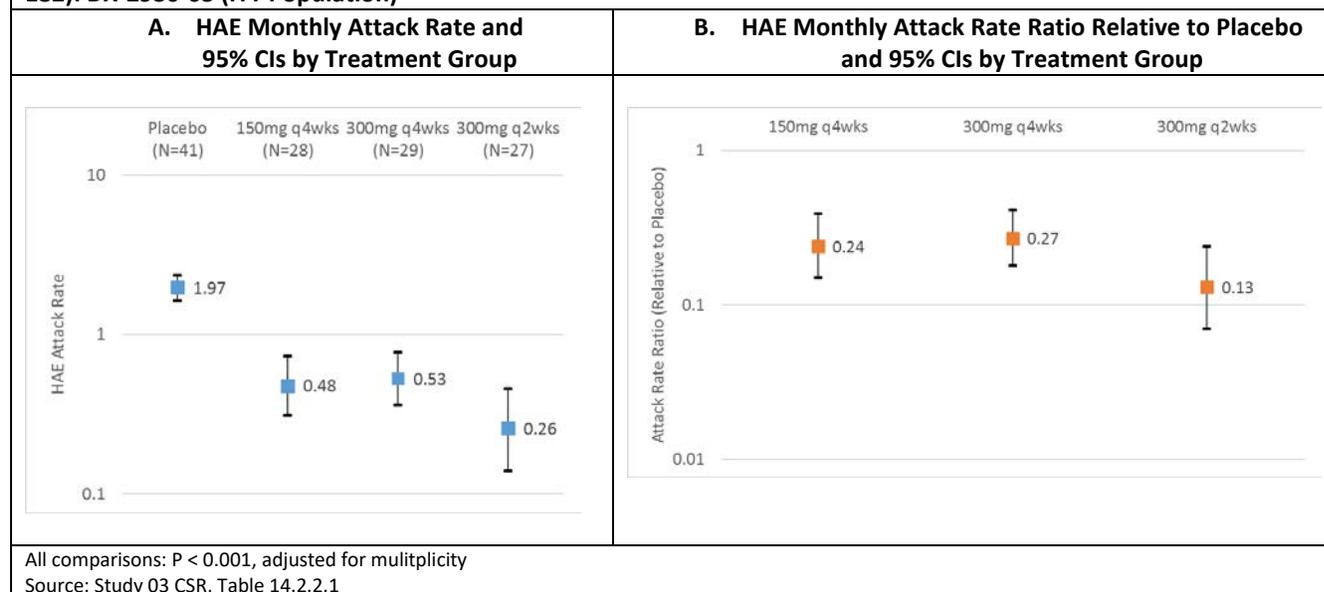


Table 27. Results of Primary and Secondary Efficacy Measures:		(b) (4) (ITT Population)		
Endpoint Statistics	Placebo (N=41)	Lanadelumab		
		150mg Q4W (N=28)	300 mg Q4W (N=29)	300 mg Q2W (N=27)
<b>Number of HAE Attacks from Day 0 to 182<sup>a</sup></b>				
LS Mean (95% CI) monthly attack rate <sup>b</sup>	1.97 (1.64, 2.36)	0.48 (0.31, 0.73)	0.53 (0.36, 0.77)	0.26 (0.14, 0.46)
(b) (4)				
Adjusted p-values <sup>c</sup>		<0.001	<0.001	<0.001
<b>Number of HAE Attacks Requiring Acute Treatment from Day 0 to 182</b>				
LS Mean (95% CI) monthly attack rate <sup>b</sup>	1.64 (1.34, 2.00)	0.31 (0.18, 0.53)	0.42 (0.28, 0.65)	0.21 (0.11, 0.40)
(b) (4)				
Adjusted p-values <sup>c</sup>		<0.001	<0.001	<0.001
<b>Number of Moderate or Severe HAE Attacks from Day 0 to 182</b>				
LS Mean (95% CI) monthly attack rate <sup>b</sup>	1.22 (0.97, 1.52)	0.36 (0.22, 0.58)	0.32 (0.20, 0.53)	0.20 (0.11, 0.39)

Table 27. Results of Primary and Secondary Efficacy Measures:		(b) (4) (ITT Population)		
Endpoint Statistics	Placebo (N=41)	Lanadelumab		
		150mg Q4W (N=28)	300 mg Q4W (N=29)	300 mg Q2W (N=27)
(b) (4)				
Adjusted p-values <sup>c</sup>		<0.001	<0.001	<0.001
Note: CI=confidence interval; SD=standard deviation; LS=least squares. Results are from a Poisson regression model accounting for over dispersion with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the treatment period as an offset variable in the model. <sup>a</sup> Model-based treatment period HAE attack rate (attacks/4 weeks). <sup>b</sup> The rate ratio is ratio of the model-based treatment period HAE attack rates. <sup>c</sup> Adjusted p-values for multiple testing. Source: revised label				

Primary and secondary endpoints calculated by the Applicant were rate ratios, with analyses incorporating recurrent events in patients who had multiple HAE attacks. We were also interested to calculate proportions of patients with at least one HAE attack by treatment, for all HAE attacks, those requiring acute therapy and those that were moderate or severe for comparison (Table 28). Proportions behaved similarly to rate ratios, with large differences between the lanadelumab arms and placebo. As illustrated here and in Figure 29, attack rate can be influenced by a few patients with particularly severe or refractory disease, especially when the sample size is relatively small.

*Reviewer note: A total of 9 unconfirmed HAE attacks were reported by 8 patients. Upon review, the investigators' decisions to categorize these events as AEs other than HAE attacks appear appropriate. There is no concern that the rate of investigator-confirmed HAE attacks differed from the actual HAE attack rate.*

Table 28. HAE Attack Frequencies by Treatment Arm: DX-2930-03 (ITT Population)				
	Placebo N=41	LAN 150 Q4W N=28	LAN 300 Q4W N=29	LAN 300 Q2W N=27
Number of HAE Attack Events	576	85	107	47
Subjects with HAE Attacks, n (%)	40 (98%)	17 (61%)	20 (69%)	15 (56%)
Number of HAE Attacks requiring acute therapy	508	56	89	38
Subjects with HAE Attacks requiring acute therapy, n (%)	39 (95%)	15 (54%)	14 (48%)	12 (44%)
Number of Moderate or Severe HAE Attacks	324	64	63	35
Subjects with Moderate or Severe HAE Attacks, n (%)	39 (95%)	15 (54%)	14 (48%)	12 (44%)
Source: Stat Reviewer, Study 03 HAE frequency check				

### Sensitivity Analysis

As stated above, patients who prematurely discontinued treatment were to remain in the study for the 26-week treatment period, a data collection practice intended to reduce the amount of missing data. If this post-discontinuation data was collected, it was not used in the applicant's analysis. It would be useful to report these types of disposition separately if they are not equal (or if they are equal, to comment that patients who discontinued treatment were not actually followed up for efficacy/safety assessments, despite what was stated in the protocol).

The tipping point analysis to measure the potential effect of missing data on the reliability of efficacy results and other planned sensitivity analyses support the robustness of the outcome of the primary endpoint analysis (Table 29). The tipping point analysis supports the robustness of the primary efficacy results considering that the tipping multiplicative factor of 35 for lanadelumab 300 mg Q2W is clinically highly implausible, in other words, patients with missing data would need to have HAE attack rates 35 times higher than those who continued to tip or reverse the results. This was expected since the evidence in the primary analysis was strong and since only 12 of 125 (9.6%) subjects prematurely discontinued the study and had missing data.

In total, the applicant included 10 subjects in the multiple imputation and tipping point analyses, even though 12 subjects in total discontinued. A subject who discontinued more than 182 days after the first dose and provided any assessment between his/her last dose date and early discontinuation date, was considered as not missing the report of HAE attack data. Subjects (b) (6) and (b) (6) satisfied these conditions and were not included in the imputation.

**Table 29. Tipping Point Analysis: Poisson regression of HAE attacks during the treatment period (Day 0-182) after missing data imputation by treatment group: DX-2930-03 (ITT Population)**

	Placebo N=41	Lanadelumab		
		150 mg q4wks N=28	300 mg q4wks N=29	300 mg q2wks N=27
Number of Subjects Missing Data <sup>a</sup> , n (%)	5 (12.2)	1 (3.6)	2 (6.9)	2 (7.4)
Value of the Tipping Point $\delta^b$		27	22	35
<b>100% of tipping point</b>				
Rate Ratio vs Placebo <sup>c</sup> (95% CI)		0.400 (0.186, 0.862)	0.495 (0.277, 0.886)	0.317 (0.121, 0.831)
p-value		0.019	0.018	0.020
<b>25% of the Tipping Point <math>\delta</math></b>				
Rate Ratio vs Placebo (95% CI)		0.278 (0.171, 0.453)	0.315 (0.208, 0.477)	0.172 (0.091, 0.323)
p-value		<0.001	<0.001	<0.001
<b>75% of the Tipping Point <math>\delta</math></b>				
Rate Ratio vs Placebo (95% CI)		0.359 (0.182, 0.707)	0.434 (0.257, 0.734)	0.267 (0.112, 0.639)
p-value		0.003	0.002	0.003
<b>150% of the Tipping Point <math>\delta</math></b>				
Rate Ratio vs Placebo (95% CI)		0.486 (0.195, 1.211)	0.619 (0.314, 1.222)	0.419 (0.139, 1.268)
p-value		0.121	0.167	0.124

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200% of the Tipping Point $\delta$				
Rate Ratio vs Placebo (95% CI)		0.573 (0.205, 1.603)	0.746 (0.349, 1.595)	0.525 (0.157, 1.762)
p-value		0.289	0.449	0.297

HAE= hereditary angioedema; ITT=intent-to-treat; NE= Non-estimated; q2wk=every 2 weeks; q4wk=every 4 weeks

<sup>a</sup> Subjects with missing data are subjects who drop out of the study early and did not complete the treatment period (Day 0 to Day 182). Number of days is calculated as 183 - the study day of the double-blind end date. Subject (b) (6) had no clinical data collected between last dose and double-blind end date, therefore last day of treatment was used in this case

<sup>b</sup> The value of  $\delta$  represents a multiplicative effect on the imputed rate of attacks for subjects who are missing data during the treatment period (Day 0 to Day 182). The tipping point is the value of  $\delta$  at which the results of the study comparison are reversed and the p-value is greater than or equal to 0.0167 ( $\alpha/3$ ) for a DX-2930 treatment arm vs. placebo comparison.

<sup>c</sup> The rate ratios are the estimates from the Poisson model after combining the estimates from the 1000 simulations using Rubin's rules.

Source: Table 14.2.2.6

Source: Applicant's Study 03 CSR, Table 17

A sensitivity analysis using the negative binomial GLM in comparison to the primary Poisson GLM to analyze the number of attacks between Day 0 and Day 182 visit was also conducted to assess whether the two methods for correcting over dispersion were consistent. As shown in Table 30, the sensitivity analysis supported the outcome of the primary endpoint analysis, resolving concern about potential over dispersion.

**Table 30. Comparison of primary analysis (Poisson GLM) with sensitivity analysis (Negative Binomial GLM): DX-2930-03 (ITT population)**

Endpoint: Number of investigator-confirmed HAE attacks from Day 0 to 182 Statistic:	Placebo (N=41)	Lanadelumab		
		150mg Q4W (N=28)	300 mg Q4W (N=29)	300 mg Q2W (N=27)
<b>Primary Efficacy with Poisson GLM:</b>				
Model-based treatment period HAE attack rate (attacks/4 weeks) <sup>b</sup>	1.967	0.480	0.526	0.257
LS Mean (95% CI)	(1.640, 2.358)	(0.313, 0.735)	(0.358, 0.771)	(0.145, 0.458)
% Change mean attack rate (vs placebo)		<b>-75.609</b>	<b>-73.271</b>	<b>-86.921</b>
% Change 95% CI		(-84.650, -61.243)	(-82.379, -59.456)	(-92.828, -76.150)
Adjusted p-values		<0.001	<0.001	<0.001
<b>Sensitivity Analysis with Negative Binomial GLM</b>				
LS Mean (95% CI)	1.934	0.500	0.481	0.256
	(1.464, 2.554)	(0.340, 0.734)	(0.330, 0.700)	(0.164, 0.399)
% Change mean attack rate (vs placebo)		<b>-74.161</b>	<b>-75.130</b>	<b>-86.780</b>
% Change 95% CI		(-83.946, -58.412)	(-84.385, -60.392)	(-92.169, -77.683)
Adjusted p-values		<0.001	<0.001	<0.001

Source: CSR DX-2930-03, Table 9 and Table 18

### Data Quality and Integrity

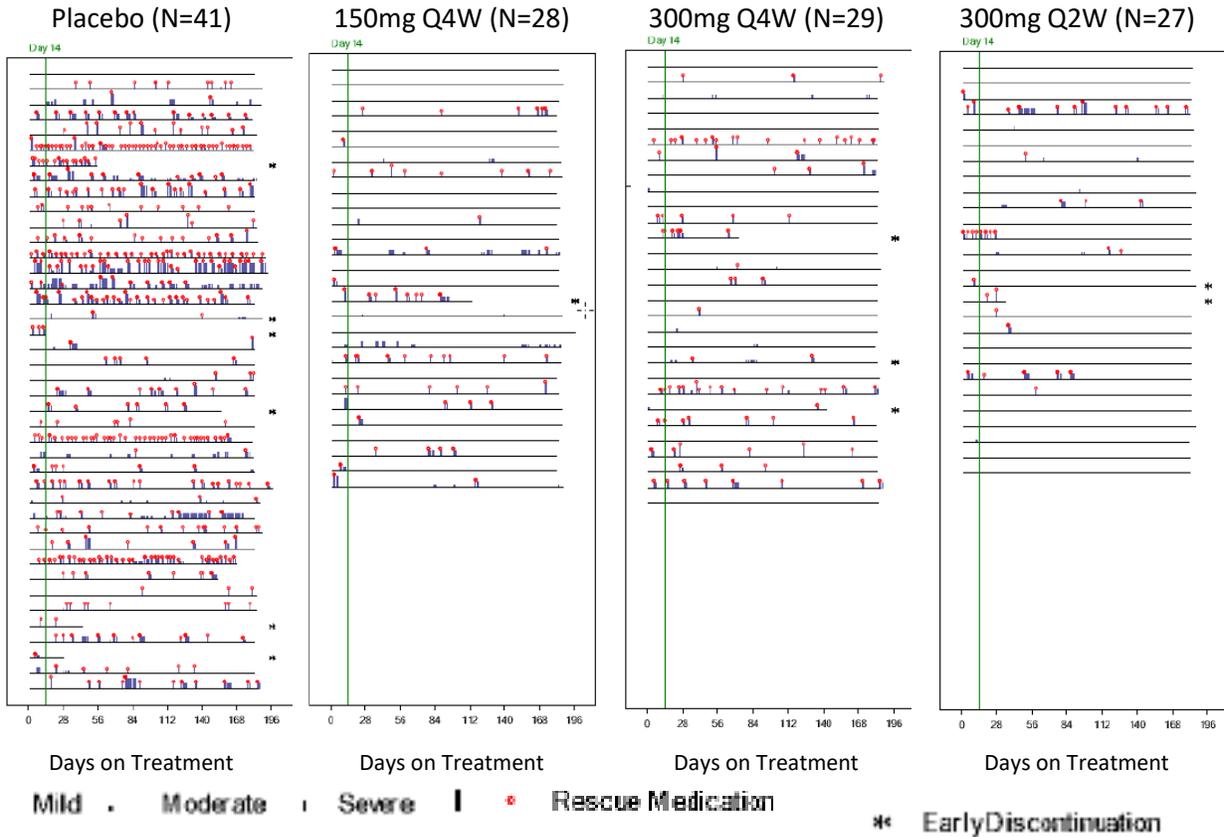
No data quality issues were identified in the review of this BLA. OSI audits of study sites 101 and 106 from trial 03 did not reveal any substantial issues related to data integrity.

### Other Efficacy Results

The applicant's post-hoc figure displaying each patients' attack duration and severity, rescue medications, and relative small number of discontinuations is a compelling summary of the

patient-level data. Whilst the applicant demarcated Day 14 as the time when the drug may be more effective, data from applicant’s Figure 29 suggests that in many patients, lanadelumab may be efficacious before Day 14 as well.

**Figure 29. Duration and severity of HAE attacks, rescue medications and early discontinuation by treatment group: DX:2930-03 (ITT Population)**



Source: Applicant’s Study 03 CSR, Figure 5

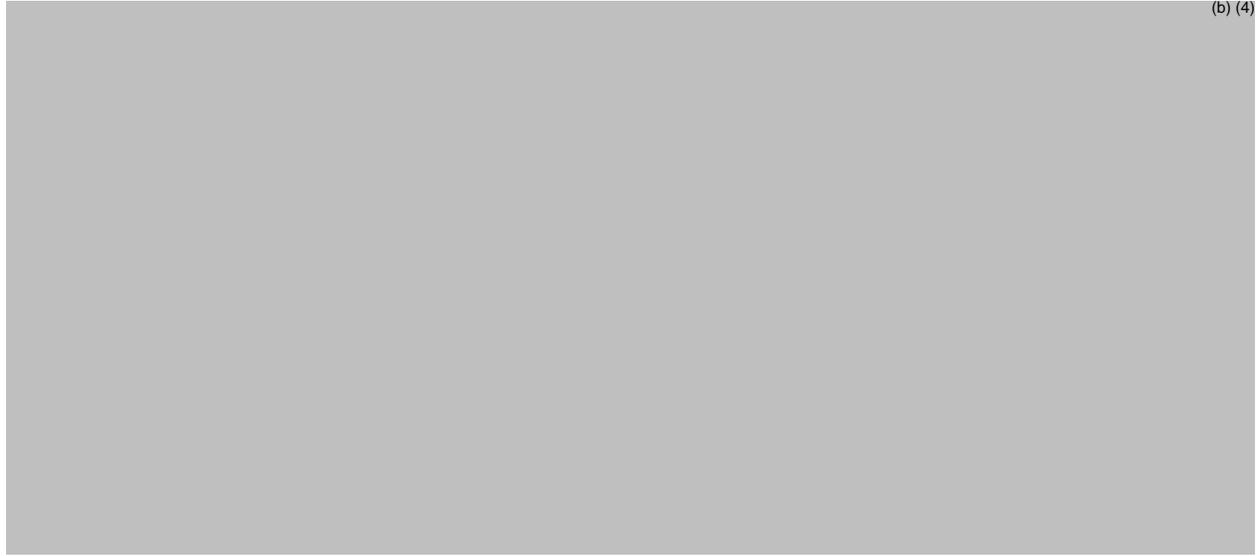


(b) (4)

These parameters were not pre-specified in the SAP primary or secondary endpoints. Percentage of attack-free days during the treatment period (Day 0 through Day 182) and achievement of investigator-confirmed HAE attack-free interval of 1 month, 3 months, or until the Day 182 visit during the treatment period (Day 0 through Day 182) were identified in the SAP as exploratory endpoints.

Descriptive statistics were calculated. The difference between placebo and all active group point estimates is consistent and substantive.

(b) (4)



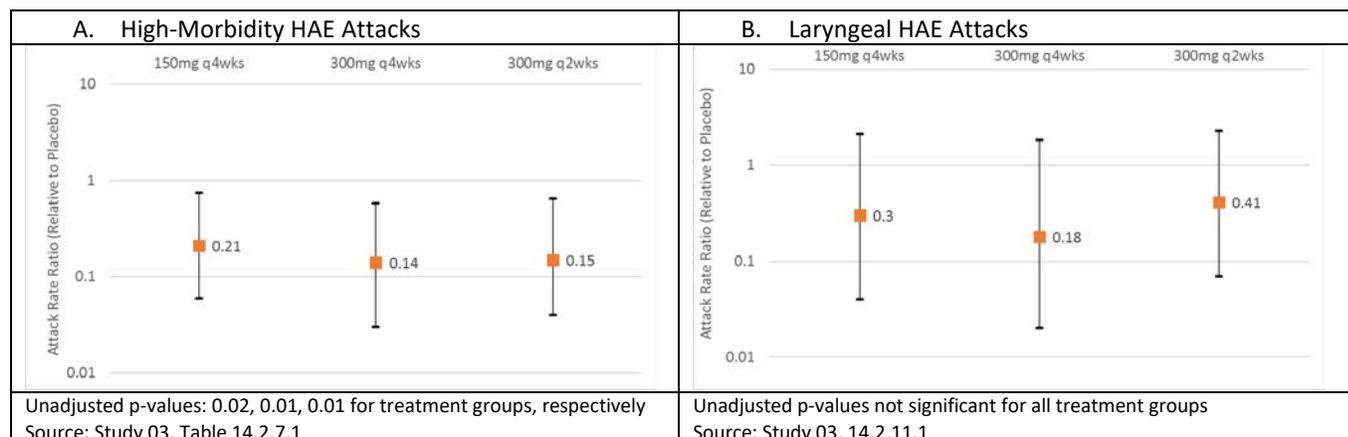
Though an exploratory endpoint, the proportion of attack-free patients is perhaps the most clinically meaningful outcome, since absent of a cure, the treatment goal in HAE is cessation of all attacks. The percentage of subjects who did not experience an attack during the 6-month treatment period provides persuasive evidence of the effectiveness of lanadelumab for prevention of acute attacks.

(b) (4)



Analyses of high morbidity attacks and laryngeal attacks were performed by the Applicant (Figure 30). High morbidity attacks were significantly lower (unadjusted for multiplicity) in active lanadelumab groups compared to placebo. Laryngeal attacks were lower compared to placebo but not significantly. This may be due to the relatively small numbers of laryngeal HAE attacks overall.

**Figure 30. Poisson regression of selected types of HAE attacks: DX-2930-03 (ITT population)**



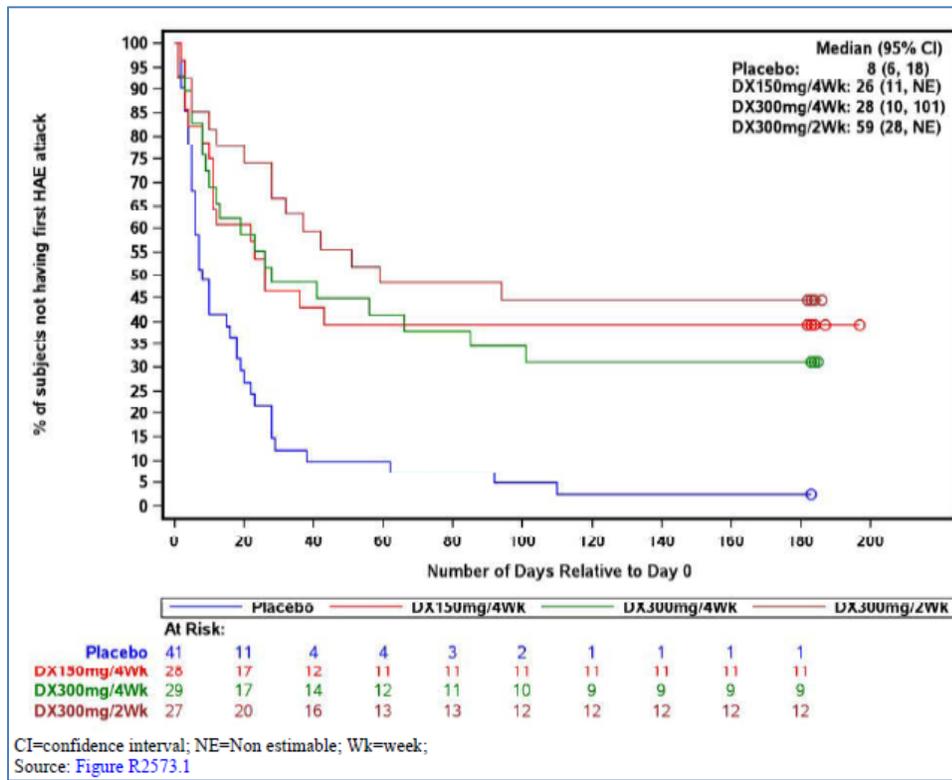
### Dose/Dose Response

The Applicant proposes a recommended dose of 300mg Q2W. All three dose regimens were clinically and statistically significant across primary and secondary efficacy parameters (multiplicity-adjusted), in addition to several exploratory endpoints. In comparison to the other two doses of 150mg Q4W and 300mg Q4W, the point estimates for 300mg Q2W regimen appears to be more efficacious for all primary and secondary endpoints, which is supportive of the Applicant’s dosing recommendation. See also applicant’s post hoc Figure 29 displaying each patients’ attack duration and severity, rescue medications, and relative small number of discontinuations. However, the lack of a clear dose-response between the two lower doses may be due to greater disease severity/higher number of non-responders in the 300 mg Q4W group. See also Section 1.3 on benefits in the context of risks and Section 6 for the Clinical Pharmacology assessment of the dose-response and exposure-response analyses.

### Onset and Durability of Response

Ad hoc analysis of time to first HAE attack from Day 0 was analyzed by the Applicant and we consider this to be the appropriate analysis. All active treatment arms had longer median time to first attack in comparison to placebo (Figure 31). The applicant prospectively analyzed truncated data at Days 14-182, Days 28-172, and Days 70-182, which is not appropriate in time-to-event analysis to condition on a post-randomization variable.

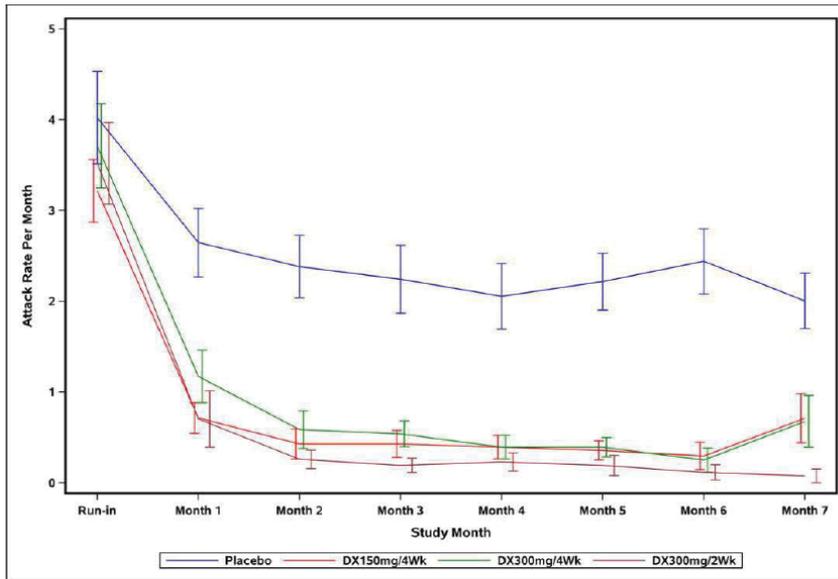
Figure 31. Time to first HAE attack, Day 0-182: DX-2930-03 (ITT Population)



Source: Applicant's Study 03 CSR, Figure 10

HAE attack rate over time was calculated as the normalized number of attacks per month. The calculation was made for each subject as the number of HAE attacks occurring during the treatment period divided by number of days the subject contributed to the treatment period (i.e., a daily rate) multiplied by 28 days. Attack rate over time demonstrated a similar pattern from the Kaplan Meier analysis in mean HAE attacks monthly rate (Figure 32), mean change from baseline HAE attack monthly rate (Figure 33), and mean percent change from baseline HAE attack monthly rate over time (Figure 34). This analysis demonstrates early onset and durability of effect.

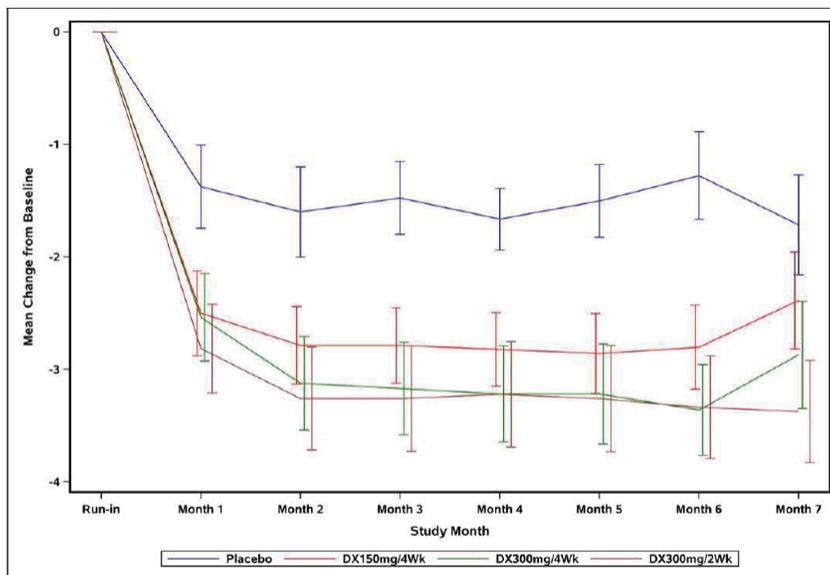
Figure 32. Mean HAE attacks monthly rate by study month and treatment group: DX-2930-03 (ITT population)



Note: Month is defined as 4 weeks or 28 days. Month 7 consists of 14 days prior to the end of the treatment period.  
Error bars indicate the standard error of the mean.  
Reference: Table 14.2.2.18.

Source: Applicant's Study 03 CSR, r2598.1

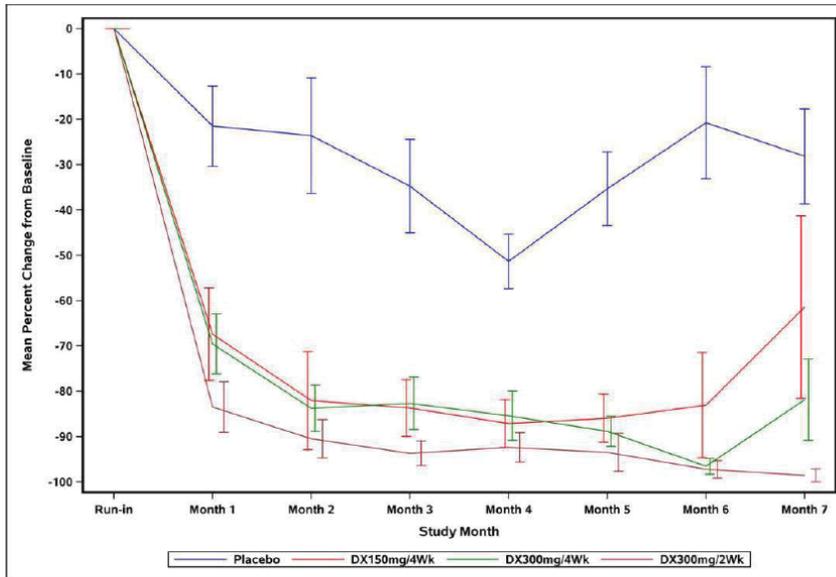
Figure 33. Mean change from baseline on HAE attacks by study month and treatment group: DX-2930-03 (ITT population)



Note: Month is defined as 4 weeks or 28 days. Month 7 consists of 14 days prior to the end of the treatment period.  
Error bars indicate the standard error of the mean.  
Reference: Table 14.2.2.18.

Source: Applicant's Study 03 CSR, r2598.2

**Figure 34. Mean percent change from baseline on HAE attacks by study month and treatment group: DX-2930-03 (ITT population)**



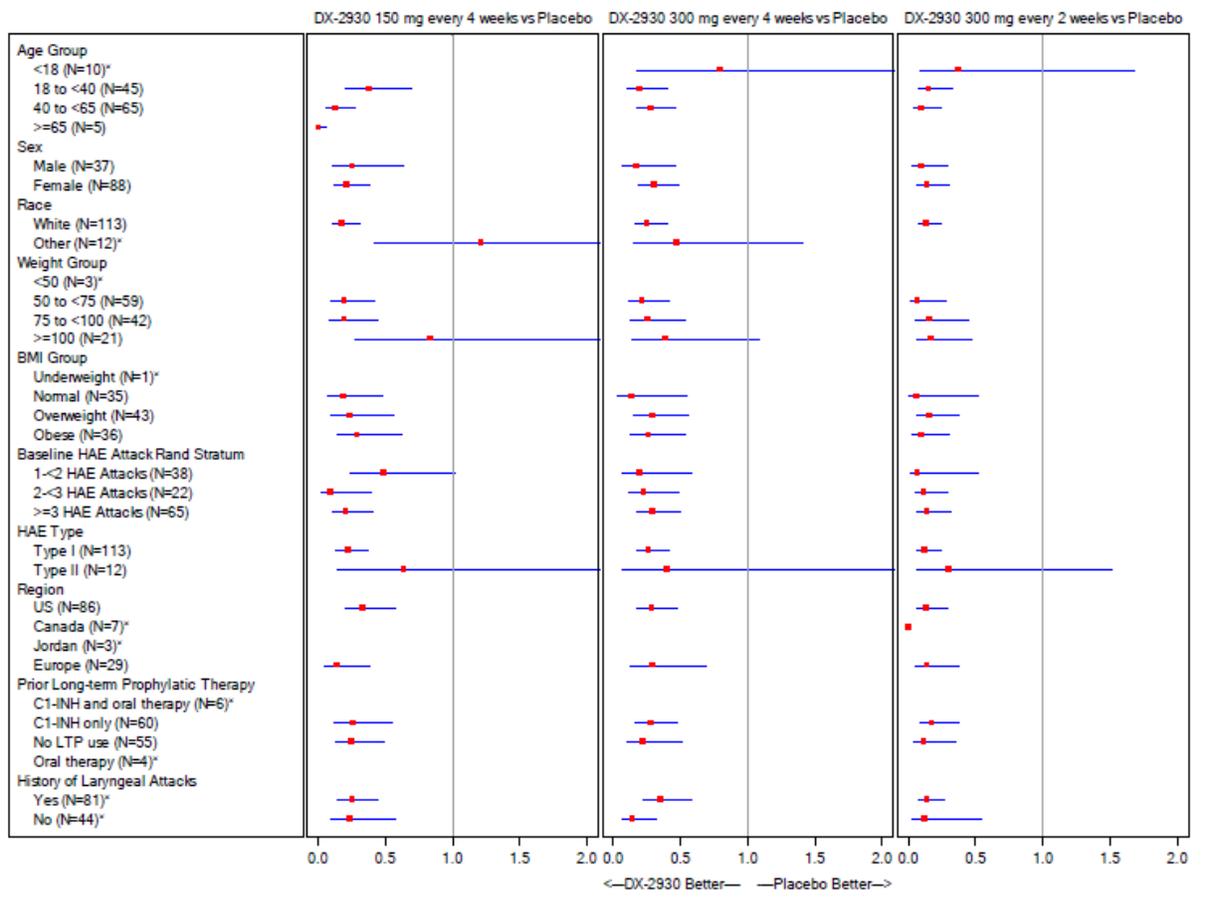
Note: Month is defined as 4 weeks or 28 days. Month 7 consists of 14 days prior to the end of the treatment period.  
Error bars indicate the standard error of the mean.  
Reference: Table 14.2.2.18.

Source: Applicant's Study 03 CSR, r2598.3

## Subpopulations

Treatment differences from placebo for various demographic parameters are shown in Figure 35. Despite relatively small sample size, the point estimates were consistent across subgroups, favoring the lanadelumab arms over placebo (with one exception in lowest dose for the non-white race subgroup, n=12). Many of the confidence intervals favored active treatment arms as well in this small study.

Figure 35. Forest plot rate ratio on HAE attacks by demographic subgroups: DX-2930-03 (ITT Population)



C1-INH= C1 inhibitor; BMI= body mass index; HAE=hereditary angioedema; ITT= intent-to-treat  
\* Rate ratio estimate was not provided for a treatment group with only one subject in the subgroup  
Source: Study DX-2930-03, Figure 19

### Efficacy Results – COA (PRO) endpoints

Quality of life was assessed using an angioedema quality of life (AE-QoL) questionnaire at seven timepoints and EQ-5D-5L at three timepoints, including baseline and end of study. (b) (4)

The EQ-5D-5L results showed no difference between placebo and lanadelumab treatment arms (b) (4)

Per the applicant’s SAP, these data were to be analyzed by ANOVA on change between baseline and final score, ANCOVA on area under the curve (AUC) for each domain and total score, and mixed effects regression for each score over time (fixed effects being treatment group and interaction of treatment by time; random effects being intercepts for subjects and slope over time).

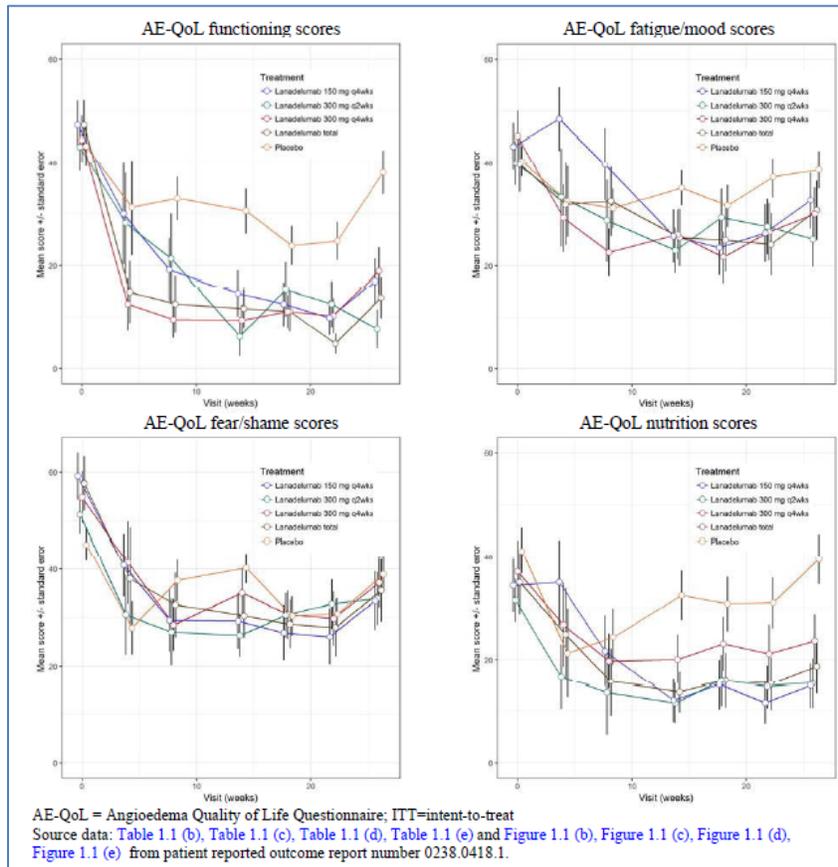
The statistically significant results (b) (4) are from the AUC analysis, based on all active treatment arms combined in comparison to placebo,

which is a different comparison from the primary, secondary, exploratory and ad hoc analyses described above for HAE attacks (i.e., each active arm compared to placebo individually).

The SAP did not specify which analysis was primary or secondary. No multiplicity adjustment was made. Results from the ANOVA show the Applicant's analysis of these pairwise comparisons had some nominally statistically significant differences from placebo for changes from baseline to final score for total and functional scores but few for fatigue/mood or nutrition scores. Results from the ANCOVA on area under the curve were similar.

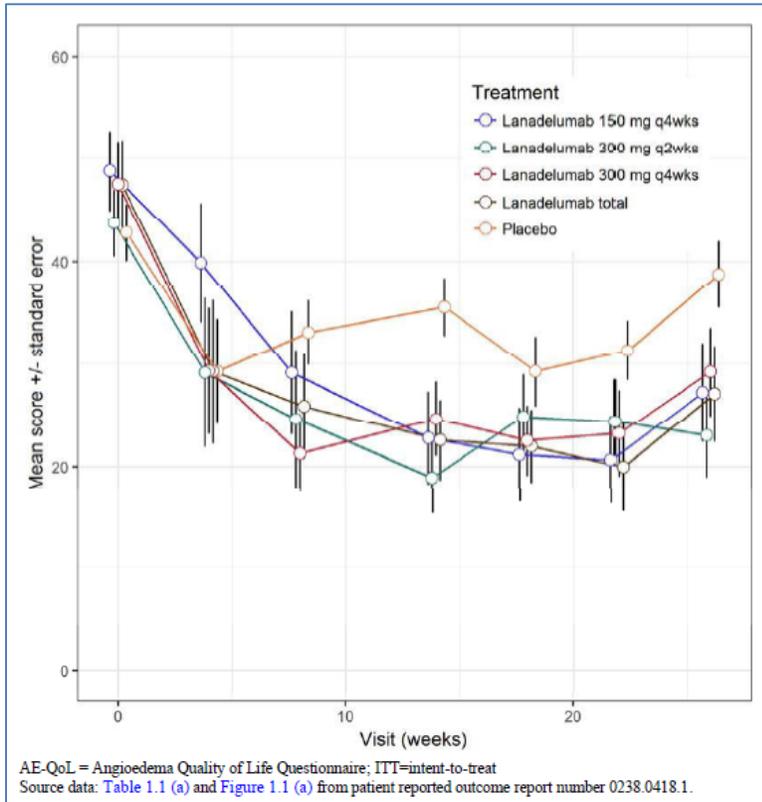
Figure 36 show some separation of placebo from active arms over time in functioning and nutrition domains. Figure 37 summarizes the four domains with a total score. Fatigue/mood and fear/shame were not significant for any treatment arm, with the exception of fear/shame at the lowest dose in the ANOVA analysis.

**Figure 36. AE-QoL domain scores at scheduled visits throughout Study 03 (ITT population)**



Source: Applicant's Study 03 CSR, Figure 38

Figure 37. AE-QoL total scores at scheduled visits throughout Study 03 (ITT population)



Source: Applicant's Study 03 CSR, Figure 37

In addition to the aforementioned statistical issues with the Applicant's analyses of the AE-QoL scores, the clinical meaningfulness of the AE-QoL results are uncertain. While the Agency recognizes the impact that HAE disease has on the quality of life of patients and caregivers,

(b) (4)

(b) (4)

### Additional Analyses Conducted on the Individual Trial

None

### 8.1.2. DX-2930-04 (HELP Extension Study)

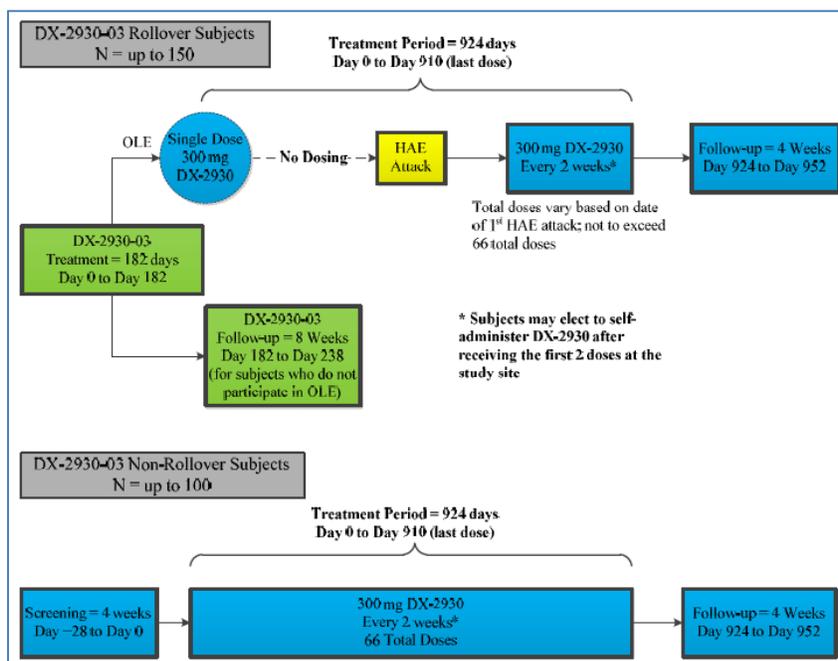
#### Trial Design

This was an open-label extension study of DX-2930-03 to evaluate the long-term safety of lanadelumab 300 mg Q2W in Types I and II HAE patients. The study consisted of two main subject cohorts: rollover subjects who completed the double-blind treatment period of Trial DX-2930-03 and non-rollover subjects who enrolled directly into the OLE study. A secondary objective of the study was to characterize the outer bounds of dosing frequency in the rollover subjects.

For rollover subjects, the last day of Trial 03 (~Day 182) was the first study visit for Study 04 (Day 0); no screening period was required. On Day 0, all rollover subjects, regardless of randomized treatment arm in the parent study, received a single open label dose of lanadelumab 300 mg. No additional lanadelumab doses were administered until their first reported and investigator confirmed HAE attack. After the first attack, subjects resumed dosing with lanadelumab 300 mg Q2W ( $\pm$  4 days) for the remainder of the 130-week (Day 910) treatment period.

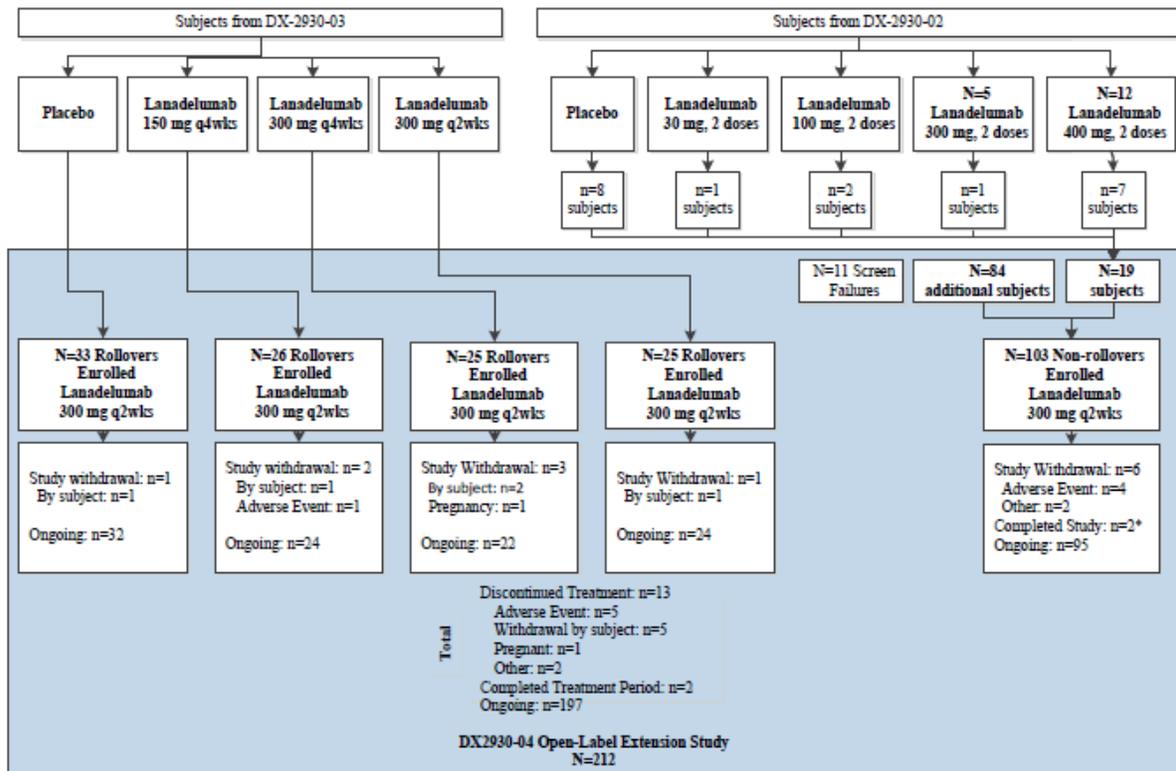
Non-rollover subjects had a screening period of up to 4 weeks, but no run-in period was required. Subjects who were on long term prophylaxis tapered off concomitant prophylaxis therapy over the first 1-2 weeks of the study while receiving lanadelumab. Subjects continued to receive lanadelumab 300 mg Q2W ( $\pm$  4 days) for the 130-week treatment duration (Day 910). A study schematic and schedule of assessments are shown below.

Figure 38. Study schematic for DX-2930-04



Source: CTP for Study DX-2930-04, Figure 1, p47

Figure 39. Overview of subject disposition in the lanadelumab development program



N, n= number of subjects

\* Subjects completed under Amendment 2 of the protocol and planned to re-enter when Amendment 3, which had a longer duration, became available.

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**Table 33. Schedule of Assessments: Study DX-2930-04**

Activities Occurring at	Treatment Period, Visit Window ± 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	27	
Non Rollover Visit	Scr <sup>a</sup>																											
Rollover Visit	-	Chk <sup>b</sup>																										
Dose Number	-	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	27
Study Day (± 4 days)	-28	0	14	28	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294	308	322	336	350	364
Informed Consent <sup>c</sup>	•	•																										
Eligibility Review <sup>d</sup>	•	•																										
Long-term prophylactic therapy cont <sup>d</sup>	•	•	•																									
DX-2930-04 Administration <sup>e, f</sup>																												
(rollover subjects) <sup>g</sup>		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
(non-rollover subjects) <sup>d</sup>		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Demographic and Medical History <sup>h</sup>	•																											
Pregnancy Test <sup>i</sup> (females)	•	• <sup>i</sup>	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Vital Signs <sup>j</sup>	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Physical Exam <sup>k</sup>	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Clinical Laboratory Testing <sup>l</sup>	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
12-Lead ECG <sup>m</sup>	•	•																										
Prior (4 wks) & Concomitant Therapy	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse Events	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
HAE Attack Data <sup>n</sup>	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Quality of Life																												
AE-QoL, EQ-5D-5L, WPAI-GH, HADS, SF-12	•																											
AECT, TSQM-9, Global Impression of Treatment Response	•																											
DX-2930 Injection Report	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
DX-2930 Self-administration & SC Injection Survey	•																											
PK, PD, ADA, <sup>o</sup> & Biomarker <sup>p</sup> Sample collection	•	•																										

Abbreviations: ADA = anti-drug antibody; AECT = Angioedema Control Test; AE-QoL = Angioedema Quality of Life; Chk = check-in; Cont<sup>d</sup> = continued; ECG = Electrocardiogram; EQ-5D-5L = EuroQoL 5-Dimensional 5-Level; HADS = Hospital Anxiety and Depression Scale; PK = Pharmacokinetic; PD = Pharmacodynamic; Scr=screening visit; SF-12 = Short Form-12; Treatment Satisfaction Questionnaire for Medication= TSQM-9; WPAI-GH = Work Productivity and Activity Impairment – General Health

- a Screening visit is for non-rollover subjects only. Screening visit can occur up to 28 days prior to first open-label dose.
- b Study site personnel will contact rollover subjects approximately every 7 days following the first dose of open-label DX-2930 to solicit for any HAE attacks not already reported. Site check-in with rollover subjects will continue until the subject receives their second open label dose.
- c Rollover subjects must sign informed consent for Study DX-2930-04 on or after Day 168 of Study DX-2930-03. Day 182 of Study DX-2930-03 is also Day 0 of Study DX-2930-04, and informed consent may be completed on this visit, if not already provided.
- d Screened non-rollover subjects (adults and adolescents) who are on LTP with C1-INH therapy for HAE can continue their current LTP until Day 8 (or Day 15) such that subjects will have received 2 (or 4) doses of C1-INH. For subjects who are on attenuated androgens (eg, danazol) or anti-fibrinolytics (eg, tranexamic acid), a similar tapering schedule is recommended. However, the taper can be prolonged by an additional week as long as androgen or anti-fibrinolytic therapy is stopped within 3 weeks of receiving the first dose of DX-2930. Since C1-INH therapy may alter the lab results of C1-INH assessments, the investigator's discretion in collaboration with Medical Monitor is advised for proper documentation of eligibility.
- e Doses are administered every 14 ± 4 days. All subjects (adolescent or adult) who are considered suitable candidates (ie, those with a physical and mental capability of learning and willing to be trained) may be allowed to self-administer DX-2930 after (1) completing appropriate training by the investigator or designee, (2) confirming their understanding, and (3) receiving the first 2 doses of DX-2930 at the study site. Subjects are then allowed to initiate home self-administration and may elect to self-administer subsequent doses of DX-2930 at the investigational site. Subjects who receive a new product format (ie, a single vial or a PFS) will receive additional training in how to self-administer with that format.
- f Site personnel will call subjects within approximately 3 days after the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.
- g Rollover subjects will not receive Dose 2 until they have experienced the first reported, investigator-confirmed attack. In addition, a minimum of 10 days is required between Dose 1 and Dose 2. If the second dose is to be administered within the accepted ± 4 day window around a scheduled study visit, this treatment visit will represent that scheduled visit unless that scheduled visit has already occurred. If that scheduled visit has already occurred, or if the second dose is to be administered outside of the accepted ± 4 day window around a scheduled visit, this visit will not replace any scheduled visit and will thus represent an acceptable, extra study visit (ie, an unscheduled visit). Regardless, at the visit in which the second open-label dose of DX-2930 is administered, the subject will undergo pre-dose assessments for vital signs, physical examination (performed in accordance with standards at the site), clinical laboratory testing, PK, PD, biomarkers and anti-drug antibody. Vital signs will be obtained at 1 hour post-dosing. As with all study visits, information will be collected on adverse events, concomitant therapy, and HAE attack data. Following Dose 2, subjects will begin regular administrations every 2 weeks.
- h For rollover subjects, demography data from DX-2930-03 will be re-entered for DX-2930-04. However, medical history reported in the DX2930-03 study will *not* be re-entered into the CRF for DX-2930-04; only *new* medical history data will be entered.
- i The pregnancy test will only be conducted in females of childbearing potential. Tests performed on Day 0 must be urine-based to confirm eligibility prior to first dose. Tests performed at screening and on indicated visits could be serum or urine-based.



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Abbreviations: AECT=Angioedema Control Test; EOS = End of Study; ET = Early Termination; PFS = prefilled syringe; Self-admin = Self-administration; Treatment Satisfaction Questionnaire for Medication = TSQM-9

NOTE: Although the first visit shown on this Schedule is at Day 378, this schedule covers the entire period following the end of the previous schedule. Certain assessments should be collected continuously throughout the study (for example, AEs) are collected continuously throughout the study.

- a Visit 68 is a site check-in call for all rollover and non-rollover subjects.
- b Subjects who terminate from the study early will undergo (if possible) all of the assessments and procedures at Visit 69, the final study visit.
- c Doses are administered every  $14 \pm 4$  days.
- d All subjects (adolescent or adult) who are considered suitable candidates (i.e., those with a physical and mental capability of learning and willing to be trained) may self-administer DX-2930 at all visits following the training described in Table 1. Subjects who receive a new product format (ie, a single vial or a (b) (4)) will receive additional training in how to self-administer with that format. Subjects may administer at home or other agreed upon location (during off-site self-administration visits; non-shaded columns). Subjects can opt to be seen in clinic for this visit.
- e Physical examinations, including weight, will be conducted for all rollover and non-rollover subjects according to the study activities schedule and in accordance with standards at the site.
- f The pregnancy test will only be conducted in females of childbearing potential. Tests performed at screening and indicated visits could be serum or urine-based.
- g There is a recommended  $\pm 15$ -minute window for all vital signs. Vital signs will be obtained prior to dosing and 1 hour after dosing. Monitoring of vital signs will not be performed for subjects who elect to self-administer away from the investigative site at optional off-site visits (indicated non-shaded columns).
- h During the study, subjects (or caregivers) are instructed to report details of the attack to the study site within 72 hours of the onset of the attack. During study visits, study site personnel will solicit for any new HAE attack information that has not already been reported to the site. Study site personnel will utilize the HAARP guidelines in order to confirm the HAE attack within 7 days.
- i Clinical laboratory testing will include Hematology, Coagulation, Serum Chemistry, and Urinalysis (urinalysis is performed as part of the clinical laboratory testing at Visits 42, 54, 66, 69).
- j Biomarker samples for C1-INH, C4, and C1q assays will be collected at Visits 34, 42, 50, 58, 66, 67, and 69.
- k Site personnel will call subjects within approximately 3 days after the planned self-administration to ensure the administration occurred, to collect AEs, concomitant medications, and to ensure all attacks have been appropriately documented.
- l Collect subject's injection reports of their experience with DX-2930 self-administration, subcutaneous administration, and prefilled syringe (if relevant) for all doses.

Source: CTP Study DX-2930-04, Tables 1 and 2, p25

## *Trial population*

The rollover population was as specified for Trial 03; all subjects who completed treatment were eligible to enroll in the OLE study 04. The non-rollover study population included adults and adolescents (12 to 17 years of age) with a confirmed diagnosis of Type I or II HAE. Eligibility criteria were similar to those in Trial 03 with the exceptions noted below:

### Key Inclusion Criteria

1. Historical baseline HAE attack rate of at least 1 attack per 12 weeks

### Key Exclusion Criteria

1. Discontinued from Trial DX-2930-03 after enrollment for any reason or significant safety concerns during Trial DX-2930-03
2. Unwilling to discontinue use of long-term prophylactic therapy for HAE within 3 weeks of starting lanadelumab (DX-2930) treatment

*Reviewer note: The main differences between the two cohorts was the required baseline attack rate (1 per month vs 1 per 3 months) and the required LTP washout prior to enrollment in study 03.*

### *Subject removal criteria*

Individual subjects were discontinued from treatment for drug-related SAEs or clinically significant AEs at the investigator's discretion.

### *Study treatments*

Lanadelumab 300 mg Q2W administered as a single 2mL injection in the upper arm, thigh, or abdomen.

- Rollover subjects: single 300 mg dose until 1<sup>st</sup> HAE attack in the OLE, then 300 mg Q2W

- Non-rollover subjects: 300 mg Q2W for entire study

Lanadelumab study drug was provided as (b) (4)  
one vial containing 300mg in 2mL. (b) (4)

(b) (4)

### *Self-administration*

All subjects who were able and willing to undergo training were allowed to self-administer treatment after receiving the first two doses of lanadelumab at the study site. Self-administered doses could be given at home or at the study site. For each self-administered dose, subjects completed an assessment of their experience which was then captured in the eCRF. Subjects also completed an assessment of their overall experience with self-administration and SC injections (as compared to IV injections) at scheduled intervals.

### *Concomitant medications*

All subjects received standard of care therapy for acute angioedema attacks during the study. Prohibited medications were the same as in Trial 03.

## **Study Endpoints**

### *Safety*

The primary objective of the OLE was to provide long-term safety data with chronic, open-label lanadelumab treatment in one dose, 300mg Q2W. Safety assessments captured in the study include: adverse events/serious adverse events, clinical labs (hematology, chemistry, LFTs, UA, coagulation, pregnancy), ECG, vital signs, physical exam, and ADA testing.

### *Efficacy*

A secondary objective of this OLE study was to characterize the outer bounds of the dosing interval as assessed by the time to first investigator-confirmed HAE attack in the rollover population. Time to 1<sup>st</sup> attack was calculated from the date/time of the first open-label lanadelumab dose. Subjects who discontinued the study prior to experiencing their 1<sup>st</sup> attack were censored at the date/time of study discontinuation. Results were summarized using Kaplan Meier methods.

Other efficacy endpoints included HAE attack information (overall rate, number requiring acute treatment, number of moderate to severe attacks, number of high morbidity attacks, percentage of attack-free subjects and days) and AE-QoL as in Trial 03.

### *Definition of Populations*

The *Safety Population* included all subjects who received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930).

- *The Rollover Safety Population* was the subset of subjects who participated in the DX-2930-03 study and received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930).

- *The Non-rollover Safety Population* was the subset of subjects who entered the DX-2930-04 study directly and received any study drug after entering the DX-2930-04 study (i.e., any exposure to open-label DX-2930).

### **Statistical Analysis Plan**

Safety was summarized during the treatment period by treatment arm of the previous study (rollover patients) and non-rollover patients who were enrolled in this study alone, in the populations as described above. Patient exposure and number and proportion of patients with adverse events (any AEs, related AEs), serious and related serious AEs, severe and related severe AEs, investigator-reported AEs of special interest, and deaths, hospitalizations and study discontinuations due to an AE were summarized by SOC and PT for the treatment period. Adverse events of special interest for lanadelumab are hypersensitivity reactions and disordered coagulation (hypercoagulability events and bleeding events).

Laboratory test results were summarized by panel type (hematology, coagulation, chemistry, urinalysis) using the Safety Population.

Efficacy objectives in this uncontrolled open label trial were exploratory, and adjunct information relative to the controlled trial. Descriptive statistics, including Kaplan-Meier estimates for time to first attack in rollover subjects were used.

No formal statistical hypothesis testing was performed. All statistical testing was considered exploratory, and all p-values considered descriptive. There was no adjustment for multiplicity and no imputation of missing data. All analyses were performed on the safety population, defined as any subject who received at least one dose of lanadelumab. For analyses performed on non-placebo rollover subjects, the treatment period was divided into two stages: dose-and-wait and regular dosing.

### **Protocol Amendments**

The Applicant amended the protocol three times with the following key changes:

#### *Amendment 1 (June 27, 2016)*

- Extended treatment period from 6 to 12 months
- Increased number of non-rollover subjects from 50 to 100 with at least 15 adolescents
- Allowed non-rollover subjects to taper long-term prophylaxis instead of prior discontinuation and washout
- Allowed self-administration after training
- Updated efficacy evaluation period to begin at Day 0 instead of Day 14
- Added interim analysis when at least 35 subjects completed 12 months of treatment
- Expanded quality of life assessments
- Added tertiary objectives: safety and efficacy in the non-rollover population switching from long term prophylaxis, breakthrough attack characteristics compared to historical baseline, subject experience with self-administration

- Added DSMB

*Amendment 2 (January 20, 2017)*

- Clarified that female rollover subjects of childbearing potential may continue to use effective contraceptives
- Removed inconsistencies in the text to accurately reflect changes made with amendment 1

*Amendment 3 (June 29, 2017)*

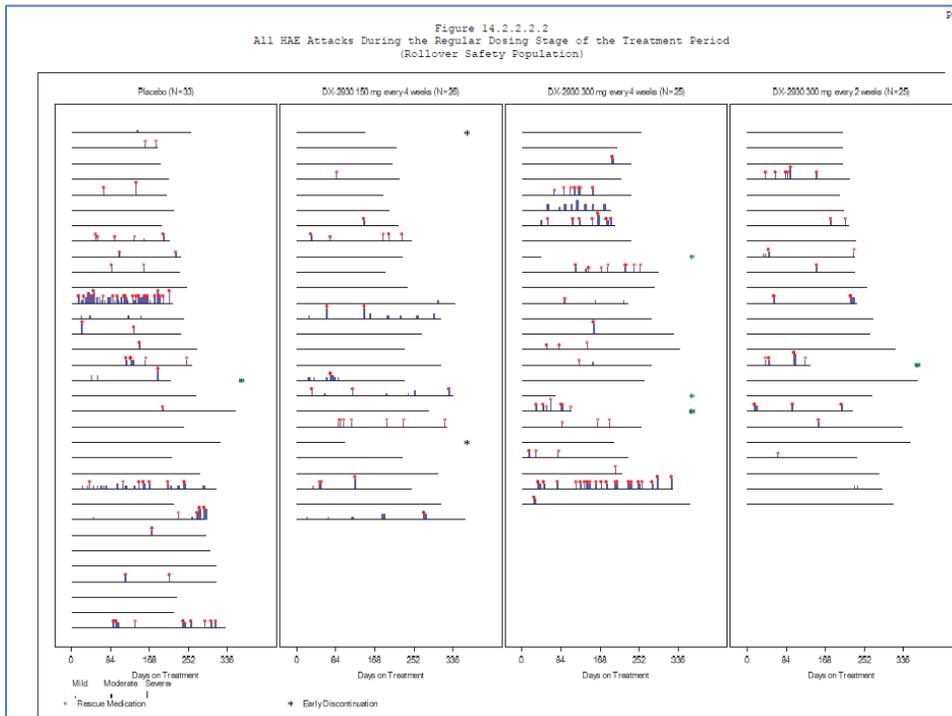
- Extended treatment period from 12 to 30 months
- Added the following tertiary objectives and endpoints: exploratory biomarkers of HAE disease activity in plasma and serum, subject response to rescue medication, treatment satisfaction questionnaire, global impression of treatment response, angioedema control test, subject experience with (b) (4)
- Included history of laryngeal attacks as a subgroup analysis

**8.1.2.1. DX2930-04 Study Results**

The primary objective of this study is safety. Efficacy results from the dose and wait period to characterize the outer bounds of dosing frequency and the overall attack rate are discussed below to provide additional support for the efficacy demonstrated in Study DX-2930-03. The remainder of results pertaining to exposure and safety are discussed in Section 8.2.

HAE attacks in those patients who were in both DX-2930-03 and DX-2930-04 are presented in Figure 40. This patient-level data shows a few subjects continued to have attacks and required rescue medication, specifically in the DX-2930-03 placebo and 300mg Q4W arms. As discussed in Section 6, the 300 mg Q4W arm from trial 03 appears to have consisted of patients with more severe disease or “non-responders”, which could explain the lack of a dose-response observed in the controlled trial. Nonetheless, the treatment effect of lanadelumab did not appear to wane over time in the majority of rollover patients in the OLE study.

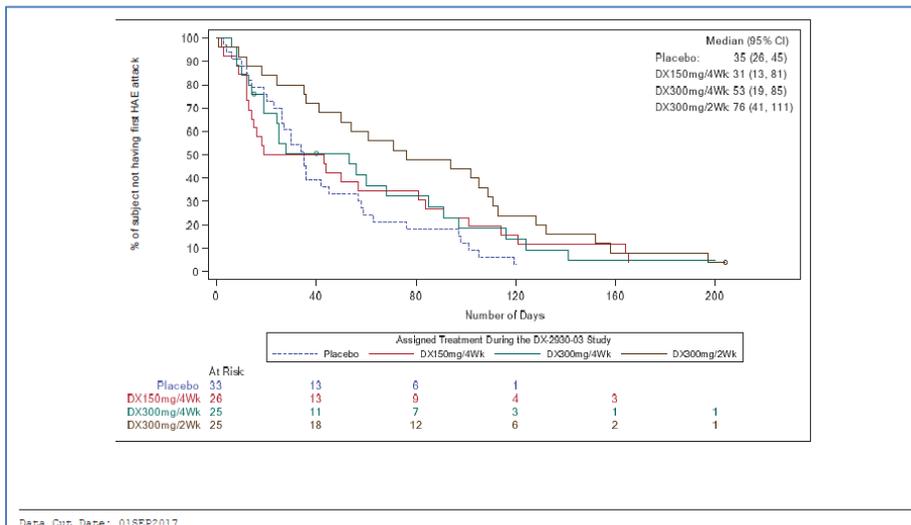
Figure 40. All HAE attacks during the OLE regular dosing stage: DX-2930-04 (Safety population)



Source: Study 04 CSR, Figure 14.2.2.2

Although complicated by the varying plasma drug concentrations at the time of rollover and receipt of the initial 300 mg dose, the ‘dose and wait’ period was intended to characterize the outer bounds of dosing frequency given that only two dosing intervals were evaluated in trial 03. The time to first HAE attack in the ‘dose and wait’ period is shown by trial 03 treatment arm in Figure 41. The median time to first attack ranged from 31 to 76 days.

Figure 41. Time to first HAE attack during OLE Dose and Wait period: DX-2930-04 (Rollover Safety population)



Source: DX-2930-04 CSR, Figure 14.2.1.1

While neither dose titration nor step-down therapy were formally evaluated in the development program, the dose-response and exposure-response analyses (discussed in detail in Section 6) suggest that after a treatment period of 4-6 months, the added benefit of more frequent Q2W dosing compared to Q4W dosing may be marginal. Using the ‘dose and wait’ period of the OLE, we may also estimate the effect of extending the dosing interval after 6 months of continuous Q2 week dosing. The table below shows the proportion of patients (grouped by study 03 randomization arm to account for varying plasma concentrations of lanadelumab upon entry) who remained attack-free at various timepoints in the ‘dose and wait’ period of the OLE (Table 34). Notably, patients who had been in the 300 Q2W treatment arm had much longer times to first HAE attack with 80% remaining attack-free at week 4. Twenty percent (5/25) of subjects in the 300 Q2W arm had an HAE attack prior to week 4; of these, three of the attacks occurred within 14 days of receiving a 300 mg dose of lanadelumab, suggesting that these patients may have more severe disease and would continue to have attacks prior to the next dose regardless of dosing frequency. Although interpretation of these post-hoc analyses is limited by small sample sizes, unblinded treatment and high degree of inter-patient variability in disease severity, the totality of data support the notion that the dosing interval might be extended in some well-controlled patients from every 2 to every 4 weeks after a period of (b) (4) 6 months without substantial loss of efficacy. The numbers are too small to identify predictive factors for who may be able to extend the dosing interval; however, the available data support what one might expect, that patients with less severe disease can likely go longer in between dosing without experiencing breakthrough attacks. Patients who had a lower baseline attack frequency and fewer attacks during study 03 were more likely to be in the group of patients who were attack-free at week 4 and beyond.

**Table 34. Proportion of patients who had their first HAE attack during the ‘dose and wait’ treatment period using Kaplan-Meier Method: DX-2930-04 (Rollover Safety Population)**

Weeks on Dose and Wait	DX-2930-03 Placebo N=33	DX-2930-03 150mg Q4W N=26	DX-29303 300mg Q4W N=25	DX-2930-03 300mg Q2W N=25
2	21.2%	34.6%	24.0%	12.0%
4	39.4%	50.0%	49.3%	20.0%
6	63.6%	50.0%	49.3%	32.0%
8	66.7%	61.5%	58.5%	40.0%
10	78.8%	65.4%	67.8%	44.0%

Source: Study DX-2930-04, Table 14.2.1.1.11

### 8.1.3. Assessment of Efficacy Across Trials

Efficacy results from the single pivotal trial, DX2930-03, serve as the basis for approval.

#### 8.1.4. **Integrated Assessment of Effectiveness**

The pivotal efficacy trial DX-2930-03 in the development program for HAE prophylaxis was adequately conducted and well-controlled. Results from this trial demonstrated substantial evidence of efficacy across multiple endpoints (e.g., monthly attack rate, rate of moderate-severe attacks, rate of attacks requiring rescue medication, attack-free rate) for all lanadelumab doses compared to placebo in patients with Type I or II HAE. The enrolled patient population is representative of a general HAE patient population with relatively frequent attacks who are likely to use and benefit from the product in clinical practice.

With regard to dose, the magnitude of treatment effect was the largest in the high dose arm (300 mg Q2W), and a recommended starting dose of 300 mg Q2W is supported by the data. However, the other two doses/dosing regimens of 300 mg Q4W and 150 mg Q4W also showed statistically significant differences from placebo. But, with numerically better efficacy in the 150 mg vs 300 mg Q4W dose group, there was no clear dose response in the controlled study.

The apparent lack of dose response can partially be explained by the limited sample size and number of patients with high attack frequency in the 300 mg Q4W treatment group. In the OLE study DX2930-04 where all patients were given the same dosing regimen of 300 mg Q2W, it appears as if more “non-responders” were initially assigned to the 300 mg Q4W arm. This imbalance may explain why the efficacy in the 300 mg Q4W arm appeared to be numerically worse than the efficacy in the 150 mg Q4W in trial DX2930-03. Furthermore, exploratory analyses conducted by the clinical pharmacology team (as discussed in detail in Section 6) showed that matched efficacy data from trial DX2930-03 to the OLE rollover patient population could be used to compare efficacy of different treatment regimens within the same patients. While there was substantial improvement in efficacy after transitioning from placebo or 150 mg Q4W dose arms to 300 mg Q2W, dose escalation from 300 mg Q4W to 300 mg Q2W only led to marginally better efficacy for the first 3-4 months. After that time period, presumably after reaching steady state, HAE attack rates were similar. Similarly, the ‘dose and wait’ period of the OLE, allowed an estimation of the effect of extending the dosing interval after 6 months of continuous Q2 week dosing. Notably, patients who had been in the 300 Q2W treatment arm had much longer times to first HAE attack with 80% remaining attack-free at week 4. Though neither dose-titration nor step-down therapy was formally evaluated in the clinical development program, our review has concluded that there is sufficient data available to support the notion that the dosing interval might be extended in some patients from every 2 to every 4 weeks after a period of (b) (4) 6 months while maintaining similar efficacy.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

All clinical studies conducted as part of the lanadelumab development program were evaluated for safety; however, given the short exposure periods and absence of additional safety findings in the phase 1 and 2 studies, the focus of this safety review is on the 26-week placebo-controlled phase 3 trial DX-2930-03. In addition, safety is supported by findings from the open-label extension (OLE) study DX-2930-04, which is reviewed separately in Section 8.2.8. The review tools used to conduct independent reviewer analyses included MAED, JMP Clinical, JMP, JReview and OCS Toolbox Demographic Tool.

Safety issues identified *a priori* include injection site reactions, hypersensitivity reactions and events of disordered coagulation (bleeding or hypercoagulable events) based on potential pharmacologic mechanism of action.

### 8.2.2. Review of the Safety Database

#### Overall Exposure

The table below shows the entire population of subjects exposed to lanadelumab in the development program for Type I or II HAE. However, as noted above, the focus of this safety review is on Trial 03 given the short exposure periods in the phase 1 and 2 studies.

Table 35. Safety database for lanadelumab

Safety Database for Lanadelumab <sup>1</sup>		
N=330		
Clinical Trial Groups	Lanadelumab <sup>2</sup> (n=268)	Placebo (n=62)
<b>Healthy Volunteers (single-dose)</b>		
DX-2930-01	24	8
<b>Controlled trials conducted for this indication</b>		
Phase 2, Types I and II HAE (two dose, dose-ranging)		
DX-2930-02	24	13
Phase 3, Types I and II HAE (pivotal trial)		
DX-2930-03	84	41
<b>Uncontrolled trials conducted for this indication (OLE)<sup>3</sup></b>		
DX-2930-04	136	--

<sup>1</sup> Individuals exposed to study drug in this development program for HAE

<sup>2</sup> Any dose/dosing regimen of Lanadelumab

<sup>3</sup> Includes placebo arm rollover patients from Study 03 who switched to lanadelumab in open label extension; does not include rollover patients who were already randomized to lanadelumab in Study 03

Controlled study drug exposure is shown in the table below.

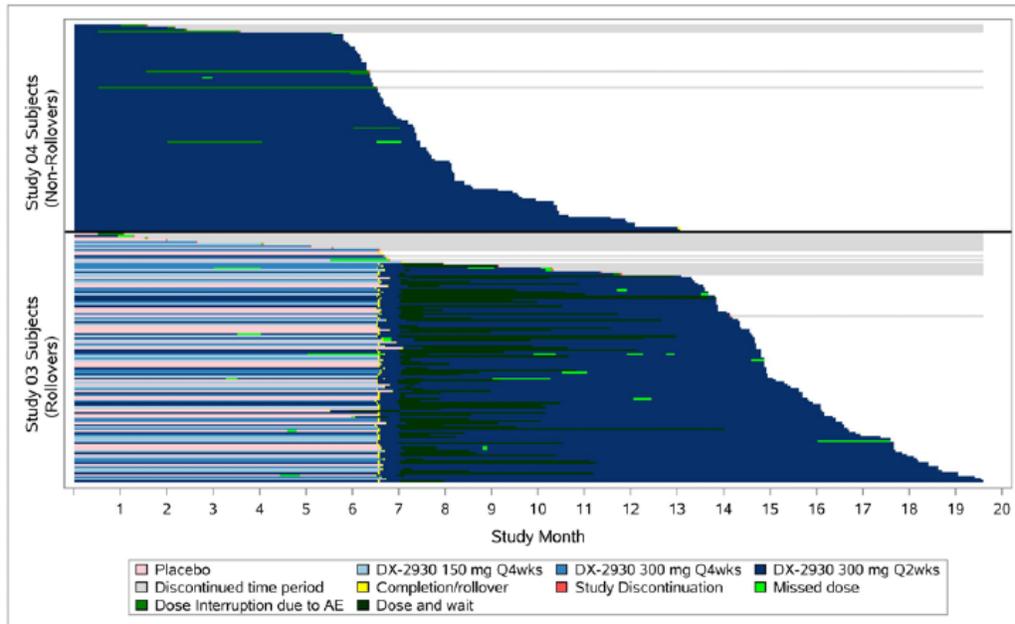
**Table 36. Duration of exposure in controlled trial DX-2930-03**

	<b>Placebo N=41</b>	<b>LAN 150 Q4 N=28</b>	<b>LAN 300 Q4 N=29</b>	<b>LAN 300 Q2 N=27</b>
<b>Number of days</b>				
Mean (SD)	152 (46)	166 (16)	162 (21)	162 (30)
Median (range)	168 (0-178)	168 (84-178)	168 (57-170)	168 (12-172)
<b>Exposure categories, n (%)</b>				
0 to <12 weeks	4 (10)	0	1 (3)	1 (4)
≥12 to <23 weeks	4 (10)	1 (4)	2 (7)	0
≥23 weeks	33 (80)	27 (96)	26 (90)	26 (96)
Reviewer generated table in JMP using ADSL dataset and TRT01P, TRTSDD and TRTEDT variables				

Assessment of drug exposure, especially in the subjects enrolled in both efficacy study DX-2930-03 and safety study DX-2930-04, was complicated by these factors: (1) subjects in the efficacy study went through a ‘dose and wait’ period of variable length depending on when they had a first HAE attack; non-rollover subjects received study drug throughout the course of the study and (2) the safety study has not yet completed so the amount of exposure for each subject varies.

The Applicant provided the lasagna plot (Figure 42) to better understand exposure of the subject population. This plot shows the duration and timing of missed doses as well as treatment discontinuations for each subject. It further characterizes the ‘dose and wait’ experience of study DX-2930-03 patients during OLE study 04, and more accurately conveys how much long-term exposure data is in the submission. There does not appear to be a treatment-related pattern in missed dosing frequency or duration.

Figure 42. Subject exposure in studies DX-2930-03 and DX-2930-04



Source: DX2930 FDA information request response, Feb 2018

### Relevant characteristics of the safety population:

The safety population is essentially the same as the efficacy population. For demographics and baseline disease characteristics, refer to Table 25 and Table 26 in Section 8.1.1.1. Of note, HAE patients with pre-existing LFT elevations  $>3x$  ULN or total bilirubin  $>2x$  ULN were excluded from enrollment. However, HAE on its own is not usually associated with liver disease unless caused by concomitant medications such as attenuated androgens; therefore, the results from these studies should generally be applicable to the broader HAE population.

### Adequacy of the safety database:

Overall, the safety database is of sufficient size and duration for a rare disease such as HAE to assess the safety of the proposed dose of lanadelumab when taken chronically. While the number of patients exposed to lanadelumab for longer than one year is limited, prolonged suppression of active plasma kallikrein is not anticipated to have deleterious effects since patients with congenital deficiency of prekallikrein (Fletcher factor deficiency) are largely asymptomatic.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

#### Issues Regarding Data Integrity and Submission Quality

No data quality issues were identified in the review of this BLA. OSI audits of study sites #101 and #106 from Trial 03 did not reveal any substantial issues related to data integrity.

#### Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events (AEs) and serious adverse events (SAEs) in the protocols. AEs were captured from signing of informed consent through the final follow up visit. Treatment emergent adverse events (TEAEs) were defined as any AE that increased in severity or that was newly developed at or after the first dose of study drug through the final follow-up visit. AEs were coded using the MedDRA dictionary version 20.0. Grading of AE severity was based on the Division of Microbiology and Infectious Diseases (DMID) Adult and Pediatric Toxicity Tables (Draft, November 2007) or as mild / moderate / severe / life-threatening (Grade 1-4). The Applicant's coding of verbatim terms to preferred terms (PTs) was appropriate. AEs were assessed by frequency, rather than rate, a method appropriate for trials of this duration. To analyze adverse events of special interest (AESI), the Applicant analyzed SMQs for hypersensitivity, bleeding, and hypercoagulable events. Abnormal coagulation tests were only reported as AEs when deemed clinically significant. HAE attacks were captured as AEs.

#### Routine Clinical Tests

Laboratory tests were obtained at time points specified in the schedule of assessments provided for each study. 12-lead ECGs were evaluated by a central reading vendor. Only clinically significant abnormalities (as determined by the investigator) in lab values, physical exam findings, or vital signs were reported as AEs.

### 8.2.4. Safety Results

#### Deaths

No deaths were reported in Trial 03.

#### Serious Adverse Events

The SAEs reported in trial 03 were primarily single events that one might expect to occur in HAE patients (e.g., hereditary angioedema attacks, catheter site infection) or that appear to be unrelated to study drug. The SAE of bipolar II disorder involved hospitalization for suicidal ideation following death of a spouse in a patient with a history of depression and anxiety. The pyelonephritis event was a complication following stent placement for a ureteral stone. Although more SAEs occurred in lanadelumab treatment groups compared to placebo, there

was no particular pattern or type of AE to suggest the numerical difference was due to study drug.

**Table 37. Nonfatal treatment-emergent SAEs: DX-2930-03**

Preferred Term (PT)	Placebo (N=41) n (%)	Lanadelumab Treatment Groups (N=84)			Total (N= 125) n (%)
		LAN 150 Q4 (N=28) n (%)	LAN 300 Q4 (N=29) n (%)	LAN 300 Q2 (N=27) n (%)	
Number of subjects with any SAE	1 (2)	--	3 (10)	2 (7)	5 (4)
Hereditary angioedema	1 (2)	--	--	1 (4)	2 (2)
Catheter site infection	--	--	--	1 (4)	1 (1)
Pyelonephritis	--	--	1 (3)	--	1 (1)
Meniscus injury	--	--	1 (3)	--	1 (1)
Bipolar II disorder	--	--	1 (3)	--	1 (1)

Source: Reviewer generated table in JMP clinical using ADSL and ADAE datasets where SAFFL=Y, TRTEMFL=Y, and AESER=Y

### Dropouts and/or Discontinuations Due to Adverse Effects

In trial 03, the number of patients who prematurely discontinued treatment due to an adverse event was 0, 1 (3.4%), and 1 (3.7%) in the lanadelumab 150 Q4W, lanadelumab 300 Q4W, lanadelumab 300 Q2W treatment groups, respectively, compared to 2 (4.9%) patients in the placebo group. The patient with LFT elevations had normal transaminase levels at screening and slight increases (AST 42 U/L and ALT 47 U/L) on Day 0, but had predisposing risk factors (obesity, history of hepatic steatosis, diabetes mellitus, and hyperlipidemia). Peak LFTs occurred at week 20 (AST 153 U/L and ALT 142 U/L) and decreased after withdrawal of lanadelumab study drug; no associated symptoms or required treatment were reported. Total bilirubin and alkaline phosphatase remained normal.

**Table 38. Premature discontinuations due to TEAE: DX-2930-03**

Unique Subject ID	Preferred Term	AE Study Start Day	SAE	# Doses Received
<b>Lanadelumab 300 Q4</b>				
DX-2930-03- (b) (6)	ALT increased AST increased	139	No	11
<b>Lanadelumab 300 Q2</b>				
DX-2930-03- (b) (6)	Hereditary angioedema (laryngeal attack)	28	Yes	2
<b>Placebo</b>				
DX-2930-03 (b) (6)	Tension headache	1	No	1
DX-2930-03 (b) (6)	Hereditary angioedema	12	No	1

Source: Reviewer generated table using ADSL and ADAE datasets in JMP and CSR subject narratives

### Significant Adverse Events

Two TEAEs of toxicity grade 4 were reported in the trial: an HAE attack in a placebo subject and the catheter site infection in a lanadelumab 300 Q2W subject (also considered in SAE). The majority of toxicity grade 3 TEAEs were single events with the exception of HAE attacks which occurred in three placebo and three lanadelumab 150 Q4W subjects each. There was no particular pattern or type of severe TEAE and no increase in frequency with higher nominal dose or more frequent dosing.

### Treatment Emergent Adverse Events and Adverse Reactions

To assess common adverse events that occurred during the treatment period in trial 03, similar/related preferred terms (PT) were pooled to determine incidence rates for each treatment group. The TEAEs occurring with  $\geq 10\%$  frequency in any lanadelumab treatment arm and greater than placebo are shown in Table 39, listed by PT.

**Table 39. Common TEAEs occurring in  $\geq 10\%$  subjects in individual lanadelumab arms and greater than placebo: DX-2930-03**

PTs and PT Groupings	Placebo (N=41) n (%)	Lanadelumab treatment groups			All LAN (N= 84) n (%)
		LAN 150 Q4 (N=28) n (%)	LAN 300 Q4 (N=29) n (%)	LAN 300 Q2 (N=27) n (%)	
Injection site reactions <sup>1</sup>	14 (34)	16 (57)	13 (45)	15 (56)	44 (52)
Upper respiratory infection <sup>2</sup>	13 (32)	3 (11)	9 (31)	12 (44)	24 (29)
Headache <sup>3</sup>	9 (22)	3 (11)	6 (21)	9 (33)	18 (21)
Rash <sup>4</sup>	3 (7)	2 (7)	3 (10)	1 (4)	6 (7)
Dizziness	0	1 (4)	3 (10)	1 (4)	5 (6)
Myalgia	0	1 (4)	0	3 (11)	4 (5)
Diarrhea	2 (5)	3 (11)	0	1 (4)	4 (5)

Source: Reviewer generated table analyzing ADSL and ADAE datasets in MAED and JReview, where SAFFL=Y and TRTEMFL=Y  
<sup>1</sup> Injection site reaction HLT, includes PTs (in order of decreasing frequency): injection site pain, injection site erythema, injection site bruising, injection site hematoma, injection site hemorrhage, injection site discomfort, injection site pruritus, injection site swelling, injection site induration, injection site paraesthesia, injection site reaction, injection site warmth, injection site edema, injection site rash  
<sup>2</sup> includes PTs: upper respiratory infection and viral upper respiratory tract infection  
<sup>3</sup> includes PTs headache, tension headache, sinus headache  
<sup>4</sup> includes PTs rash, rash maculopapular, rash erythematous

The risk difference in injection site reactions between lanadelumab treatment arms and placebo was primarily driven by injection site pain; however, injection site erythema and bruising were also common.

Of note, hereditary angioedema TEAEs occurred more frequently in the placebo group than lanadelumab groups further confirming the primary endpoint analysis.

## Laboratory Findings

Routine clinical testing included hematology, serum chemistry with liver function tests, coagulation, and urinalysis. Liver function tests and coagulation tests are discussed in detail below. Otherwise, there were no clinically significant differences between lanadelumab and placebo groups in laboratory parameters measured during the trial.

### Liver function tests

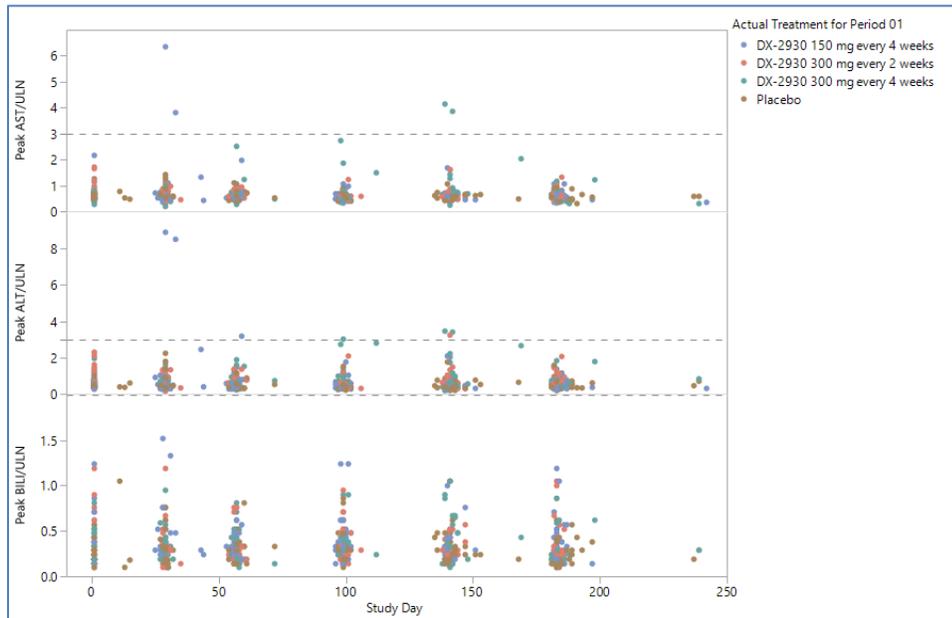
The table below shows the number of subjects with maximum elevations in AST/ALT >3x ULN and total bilirubin >2x ULN. There were no potential Hy's law cases in the program. In addition, two subjects had TEAEs of AST and ALT increased (one in 300 mg Q2W and one in 300 mg Q4W). The 300 mg Q4W subject is included in the table below and was also described in the section on premature treatment discontinuations. The other subject had elevations below 2x ULN, and thus is not included in the table below. Although there was no apparent dose dependency with this small sample size, LFT elevations were only observed in the lanadelumab treatment groups.

**Table 40. Maximum LFT parameter elevations: DX-2930-03**

Lab parameter (maximum elevation)	Placebo (N=41) n (%)	LAN 150 Q4 (N=28) n (%)	LAN 300 Q4 (N=29) n (%)	LAN 300 Q2 (N=27) n (%)	All LAN (N=84) n (%)
<b>ALT</b>					
>3x to ≤5x ULN	0	0	3 (10)	1 (4)	4 (5)
>5x to ≤8x ULN	0	0	0	0	0
>8x to ≤10x ULN	0	1(4)*	0	0	1 (1)
<b>AST</b>					
>3x to ≤5x ULN	0	0	1 (3)	0	1 (1)
>5x to ≤8x ULN	0	1 (4)*	0	0	1 (1)
<b>Total Bilirubin</b>					
>2x ULN	0	0	0	0	0
Total subjects	0	1 (4)	3 (10)	1 (4)	5 (6)
Source: Reviewer generated table using JMP clinical analyses of LB dataset ULN=upper limit of normal *Same subject					

The figure below shows the peak AST, ALT, and total bilirubin measurement (relative to ULN) for each subject by treatment group at each study visit. Transaminase elevations began to appear after approximately 1 month on study drug and continued to occur throughout the study with no particular pattern of onset.

**Figure 43. Peak LFT parameter by subject and study day: DX-2930-03**



Source: Reviewer generated table in JMP Clinical using ADSL and LB datasets

### Coagulation tests

Because of the potential for lanadelumab to affect the intrinsic coagulation pathway based on its pharmacologic mechanism of action, coagulation tests were evaluated in trial 03. While several patients had aPTT measurements above the ULN of 39.9 sec, including four placebo, three lanadelumab 150 Q4W, nine lanadelumab 300 Q4W, and eleven lanadelumab 300 Q2W, most had prolongations of 10 seconds or less. Only one patient (lanadelumab 300 Q2W) had prolongation of aPTT >1.5x ULN at week 8 with normal measurements at all other visits. As expected, there was no difference in INR values between treatment groups. Two patients (one placebo and one lanadelumab 300 Q4W) had single INR values between 2.0 and 3.0 (but less than 2x ULN). All other INR elevations were  $\leq 2$ . As noted above, there were no bleeding or hypercoagulable adverse events associated with any abnormal coagulation test result. Vital Signs **APPEARS THIS WAY ON ORIGINAL**

No substantial or clinically meaningful shifts from baseline in mean or median vital signs (SBP, DBP, pulse, respiratory rate, temperature) were observed with lanadelumab treatment across visits in the trial.

### Electrocardiograms (ECGs)

No substantial or clinically meaningful ECG trends associated with lanadelumab treatment were identified in the development program. During trial 03, ECGs obtained at screening and baseline (pre-dose Visit 1), during the active treatment period on study days 56 and 144, and post-treatment on study day 182 (Visit 14) were evaluated by a central reader. Analysis was based on ECG parameters obtained at baseline (Visit 1) and during treatment using reasonable threshold criteria, and no safety signals emerged. Cardiovascular TEAEs related to ECG findings

were rare and generally balanced between treatment groups.

## **QT**

Based on the reassuring nonclinical and early clinical findings, the low risk for QT prolongation with a monoclonal antibody, and the serial ECG monitoring in study 03, FDA's IRT team did not require a separate QTc study in the HAE population. The serial ECG results from trial 03 showed no meaningful effect of lanadelumab on the QTc interval.

## **Immunogenicity**

In trial 03, a total of 10/84 (12%) lanadelumab-treated patients and 2/41 (5%) placebo-treated patients developed a treatment emergent positive anti-drug antibody (ADA) test (or increased ADA titer in case of pre-existing ADA) on at least one occasion. Low baseline ADA titers were detected in 3 lanadelumab and 1 placebo-treated patient; one of these lanadelumab patients had an increase in titers post-treatment and is counted in the number of positive ADA samples above. Neither ADA positivity nor ADA titer appear to be dose-related. Two of the ADA samples were classified as neutralizing (both lanadelumab 150 Q4W patients). The presence of ADA or neutralizing ADA was not associated with a difference in PK/PD, efficacy or safety when compared to subjects with negative ADA.

### **8.2.5. Analysis of Submission-Specific Safety Issues**

Pre-specified adverse events of special interest (AESI) included injection site and hypersensitivity reactions and bleeding/hypercoagulable events. These AESIs were prospectively evaluated due to theoretical risks rather than potential safety concerns from the nonclinical or early clinical program.

#### **Injection site reactions**

These events are described under common adverse reactions.

#### **Hypersensitivity reactions**

One patient in the lanadelumab 300 Q2W group reported two events of "hypersensitivity" following the 3<sup>rd</sup> and 4<sup>th</sup> doses on Days 29 and 42, respectively, that consisted of injection site reaction and itchiness and tingling of the tongue. No progression of symptoms occurred; the first episode was treated with paracetamol while the second episode did not require treatment and self-resolved. The patient completed treatment in trial 03 and enrolled in the OLE. While there were adverse events of urticaria and drug hypersensitivity reported in two separate patients as well, neither event appeared to be related to study drug based on the subject narratives. No cases of anaphylaxis were identified in the development program.

## **Disordered coagulation**

There were no reports of adverse events related to bleeding or hypercoagulability in trial 03. Results from coagulation tests are described under laboratory findings.

### **8.2.6. Safety Analyses by Demographic Subgroups**

The OCS Analysis Toolbox DM Tool and JReview risk assessment tools were used to analyze safety in trial 03 by the following demographic subgroups: sex, age, race, ethnicity, region, baseline HAE attack rate group, prior LTP use, and HAE type. Given the small number of patients within each subgroup, all lanadelumab treatment groups were combined. This review did not identify a meaningful difference in overall TEAEs between lanadelumab and placebo treatment within any subgroup. Of the common TEAEs occurring in lanadelumab-treated patients, injection site reactions were reported in a higher proportion of females than males (60% vs 37%) and upper respiratory infections were reported in a higher proportion of males than females (40% vs 22%). However, the relatively low frequency of other TEAEs, SAEs and adverse dropouts in addition to the small number of subjects within certain subgroups made it difficult to draw any further conclusions regarding an imbalance in safety based on demographic or disease characteristics.

### **8.2.7. Specific Safety Studies/Clinical Trials**

Study DX-2930-04 is the open label extension (OLE) study for subjects who completed trial 03 and is currently ongoing. Uncontrolled safety data from this study provides support for the long-term use of lanadelumab for the prevention of HAE attacks. An overview of the study protocol is provided in Section 8.1.2, and descriptive results for the time to first attack for rollover patients during the 'dose and wait' period is provided in Section 8.1.2.1. This section will focus on the safety results available from the OLE study 04 including the 120-day safety update through the data cutoff of January 1, 2018.

## **Disposition**

Most subjects remain enrolled in the study with a larger number of adverse drop outs in the non-rollover cohort than the rollover cohort as one might expect. Two premature discontinuations have been re-categorized as "adverse events" instead of "withdrawal by subject" based on the specific reasons provided for withdrawal: injection site reactions and constipation/right calf numbness/lack of efficacy. The remainder of reasons cited for "withdrawal by subject" were inability to travel to study site, inability to adhere to protocol contraceptive requirements, lack of efficacy, and reason unknown. The premature discontinuations due to "other" were for lack of efficacy and subject non-compliance/physician decision.

**Table 41. Disposition of subjects: DX-2930-04**

	Non-rollover	Rollover	Total
Safety population	103 (100)	109 (100)	212 (100)
Ongoing treatment	95 (92)	100 (92)	195 (92)
Prematurely discontinued treatment	8 (8)	9 (8)	17 (8)
Adverse event	6 (6)	2 (2)	8 (4)
Withdrawal by subject <sup>1</sup>	0	6 (6)	6 (3)
Pregnancy	0	1 (1)	1 (1)
Other <sup>2</sup>	2 (2)	0	2 (1)

Source: Reviewer generated table using ADSL dataset in JMP Clinical  
<sup>1</sup>One non-rollover and one rollover subject recoded to adverse event as reason for premature discontinuation  
<sup>2</sup>Lack of efficacy and non-compliance/physician decision

The demographics and baseline disease characteristics for patients in the OLE study 04 are largely similar to those in trial 03 with the exception of baseline HAE attack rate. Given the less stringent eligibility requirements for number of HAE attacks to enter the OLE, the non-rollover cohort had a history of fewer HAE attacks and potentially a milder disease phenotype than the rollover cohort.

**Table 42. Subject demographics: DX-2930-04**

Demographic Parameters	Non-rollover (N=103) n (%)	Rollover (N= 109) n (%)	Total (N=212) n (%)
<b>Sex</b>			
Male	35 (34)	34 (31)	69 (33)
Female	68 (66)	75 (69)	143 (67)
<b>Age</b>			
Mean years (SD)	39 (17)	41 (15)	40 (16)
Median (years)	39	43	42
Min, max (years)	12, 75	12, 73	12, 75
<b>Age Group</b>			
< 18 years	13 (13)	8 (7)	21 (10)
≥ 18 to <65 years	85 (83)	95 (87)	180 (85)
≥ 65 years	5 (5)	6 (5)	11 (5)
<b>Race</b>			
White	99 (96)	99 (91)	198 (93)
Black or African American	2 (2)	8 (7)	10 (5)
Asian	0	1 (1)	1 (0.5)
American Indian or Alaskan Native	0	1 (1)	1 (0.5)
Multiple	1 (1)	0	1 (0.5)
Other	1 (1)	0	1 (0.5)
<b>Ethnicity</b>			
Hispanic or Latino	5 (5)	8 (7)	13 (6)
Not Hispanic or Latino	97 (94)	101 (93)	198 (93)
Unknown	1 (1)	0	1 (0.5)
<b>Region</b>			
United States	74 (72)	73 (67)	147 (70)
Rest of the World			
Canada	7 (7)	6 (6)	13 (6)
Europe	12 (12)	27 (25)	39 (18)

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Demographic Parameters	Non-rollover (N=103) n (%)	Rollover (N= 109) n (%)	Total (N=212) n (%)
Jordan	10 (10)	3 (3)	13 (6)

Source: Reviewer generated table using ADSL dataset in JMP Clinical, where SAFFL=Y

**Table 43. Baseline disease characteristics: DX-2930-04**

Baseline Characteristics	Non-rollover (N=103) n (%)	Rollover (N= 109) n (%)	Total (N=212) n (%)
<b>Weight (kg)</b>			
Mean (SD)	81 (26)	80 (22)	81 (24)
Median	76	76	76
Min, max	44, 178	37, 150	37, 178
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean (SD)	28 (8)	28 (7)	28 (7)
Median	26	27	27
Min, max	18, 50	17, 55	17, 55
<b>Weight Group (kg)</b>			
<50	4 (4)	3 (3)	7 (3)
50 to <75	44 (43)	51 (47)	95 (45)
75 to <100	34 (33)	37 (34)	71 (34)
≥100	21 (20)	18 (17)	39 (18)
<b>HAE Type</b>			
Type I	89 (86)	100 (92)	189 (89)
Type II	12 (12)	9 (8)	21 (10)
Unspecified	2 (2)	0	2 (1)
<b>Age at Onset (years)</b>			
Mean (SD)	12 (7)	13 (10)	13 (9)
Median	11	12	12
Min, max	1, 43	1, 49	1, 49
<b>Baseline HAE Attack Rate/Month<sup>1</sup></b>			
Mean (SD)	3 (3)	4 (2)	3 (3)
Median	2	3	2
Min, max	0, 15	1, 14	0, 15
<b>Baseline HAE Attack Rate Group</b>			
<1 attack/month	25 (24)	0	25 (12)
1 to <2 attacks/month	39 (38)	35 (32)	74 (35)
2 to <3 attacks/month	11 (11)	19 (17)	30 (14)
≥3 attacks/month	28 (27)	55 (51)	83 (39)
<b>Primary HAE Attack Location</b>			
Abdominal	12 (12)	23 (21)	35 (17)
Abdominal/Peripheral	61 (59)	47 (43)	108 (51)
Laryngeal/Abdominal	4 (4)	1 (1)	5 (2)
Laryngeal/Abdominal/Peripheral	15 (15)	18 (17)	33 (16)
Laryngeal/Peripheral	4 (4)	2 (2)	6 (3)
Peripheral	7 (7)	18 (17)	25 (12)
<b>History of laryngeal attacks</b>	63 (61)	67 (62)	130 (61)
<b>Prior LPT therapy</b>			
C1-INH only	53 (52)	53 (49)	106 (50)
Androgens only	8 (8)	3 (3)	11 (5)
Anti-fibrinolytics only	0	1 (1)	1 (0.5)
Androgens and C1-INH	1 (1)	4 (4)	5 (2)
Anti-fibrinolytics and C1-INH	1 (1)	0	1 (0.5)
Androgens, Anti-fibrinolytics, and C1-INH	0	1 (1)	1 (0.5)
None	40 (39)	47 (43)	87 (41)

Source: Reviewer generated table using ADSL dataset in JMP Clinical, where SAFFL=Y  
<sup>1</sup>Derived from baseline HAE attack rate in DX-2930-03 for rollover subjects and for reported HAE attack rate in past 3 months divided by 3 for non-rollover subjects

## Exposure

Combined exposure from trial 03 and the OLE study 04 is discussed above in Section 8.2.2. The 120-day safety update provides an additional 4 months of exposure. The table below shows exposure through the 120-day safety update with the 'dose and wait' period excluded.

**Table 44. Lanadelumab exposure through 120-day safety update excluding 'dose and wait' period: DX-2930-04**

	150 Q4 → 300 Q2 (N=28)	300 Q4 → 300 Q2 (N=29)	300 Q2 → 300 Q2 (N=27)	PBO → 300 Q2 + Non-rollovers (N=136)	All LAN treated patients (N=220)
<b>Number of months</b>					
Mean (SD)	16.9 (5)	15.6 (6)	16.4 (5)	11.6 (3)	13.4 (4)
Median	18	18	18	12	13
Min, Max	4, 24	3, 24	1, 23	2, 17	1, 24
<b>Exposure category, n (%)</b>					
1 to <6 months	1 (4)	2 (7)	1 (4)	4 (3)	8 (4)
≥6 to <12 months	4 (14)	5 (17)	3 (11)	76 (56)	88 (40)
≥12 to <20 months	15 (54)	19 (66)	21 (78)	56 (41)	111 (50)
≥20 months	8 (29)	3 (10)	2 (7)	0	13 (6)
Source: Adapted from Table R6014 in response to IR dated 6/18/18					

## Adverse Events

No deaths were reported in the OLE study.

### Nonfatal SAEs

Serious non-fatal adverse events that occurred during the OLE are shown in the table below. Events were coded as serious due to hospitalization, but were single events that were unrelated to study treatment. Most events were secondary to pre-existing conditions.

**Table 45. Nonfatal SAEs in OLE DX-2930-04**

MedDRA SOC and Preferred Term	Non-rollover N=103 n (%)	Rollover N=109 n (%)	Total N=212 n (%)
<b>Number of subjects with any SAE</b>	<b>4 (4)</b>	<b>8 (7)</b>	<b>12 (6)</b>
Congenital, familial and genetic disorders			
Hereditary angioedema	1 (1)	1 (1)	2 (1)
Gastrointestinal disorders			
Anal fissure	1 (1)	0	1 (1)
Upper gastrointestinal haemorrhage	0	1 (1)	1 (1)
Blood and lymphatic system disorders			
Hypochromic anemia	0	1 (1)	1 (1)
Infections and infestations			
Gastroenteritis	0	1 (1)	1 (1)
Injury, poisoning and procedural complications			
Accidental exposure to product	0	1 (1)	1 (1)
Incision site inflammation	1 (1)	0	1 (1)
Wound dehiscence	1 (1)	0	1 (1)

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Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis	0	1 (1)	1 (1)
Lumbar spinal stenosis	0	1 (1)	1 (1)
Systemic lupus erythematosus	1 (1)	0	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibrosarcoma	1 (1)	0	1 (1)
Psychiatric disorders			
Suicidal ideation	0	1 (1)	1 (1)
Vascular disorders			
Lymphoedema	0	1 (1)	1 (1)

Source: Reviewer generated table using ADSL dataset in JMP Clinical, where SAFFL=Y, TRTEMFL=Y, AESER=Y

AEs leading to discontinuation

Adverse events leading to premature treatment discontinuation are outlined in the table below. As in trial 03, a few subjects were discontinued due to transaminase elevations; however, these elevations were asymptomatic and confounded by co-morbidities such as history of elevated LFTs, hepatic steatosis and obesity (subject (b) (6)) or by other factors such as exercise and muscle injury in the case of subject (b) (6) who had corresponding CPK elevation. Hypersensitivity events were primarily localized and limited to skin symptoms. No cases of anaphylaxis were identified in the program. The event of pneumonia and upper GI hemorrhage which was also reported as an SAE was due to caustic chemical ingestion.

**Table 46. Adverse events leading to premature treatment discontinuation: DX-2930-04**

Unique Subject ID	Preferred Term	AE Study Start Day	SAE	# Doses Received
<b>Non-rollover cohort</b>				
DX-2930-02	(b) (6) Injection site papule	11	N	2
DX-2930-04	AST increased	1	N	1
	ALT increased	1	N	
DX-2930-04	AST increased	155	N	11
	ALT increased	127	N	9
	CPK increased	155	N	11
DX-2930-04	Hypersensitivity	45	N	4
DX-2930-04	Hypersensitivity	5	N	1
<b>Rollover cohort</b>				
DX-2930-03	(b) (6) Pneumonia	147	N	10
	Upper gastrointestinal hemorrhage	143	Y	

Source: Reviewer generated table using ADSL and ADAE datasets in JMP and CSR subject narratives

**Common TEAEs**

Below are the TEAEs occurring with a frequency of  $\geq 10\%$  in either of the cohort arms or overall. No additional common TEAEs were identified following extended use in the OLE study that were not observed in Trial 03. Results from the OLE were similar with regard to frequently reported TEAEs ( $\geq 5\%$  incidence) in the overall population; however, injection site reactions were more common in the non-rollover subjects.

**Table 47. Common TEAEs occurring in ≥5% of overall study population: DX-2930-04**

PTs and PT Groupings	Non-rollover N=103 n (%)	Rollover N= 109 n (%)	Total N=212 n (%)
Hereditary angioedema	53 (51)	107 (98)	160 (75)
Injection site reactions <sup>1</sup>	57 (55)	45 (41)	102 (48)
Upper respiratory infection <sup>2</sup>	41 (40)	52 (48)	93 (44)
Headache <sup>3</sup>	19 (18)	25 (23)	44 (21)

Source: Reviewer generated table analyzing ADSL and ADAE datasets in MAED and JReview, where SAFFL=Y and TRTEMFL=Y  
<sup>1</sup> Injection site reaction HLT, includes PTs (in order of decreasing frequency): injection site pain, injection site erythema, injection site bruising, injection site hematoma, injection site hemorrhage, injection site discomfort, injection site pruritus, injection site swelling, injection site induration, injection site paraesthesia, injection site reaction, injection site warmth, injection site edema, injection site rash  
<sup>2</sup>includes PTs: upper respiratory infection and viral upper respiratory tract infection  
<sup>3</sup>includes PTs headache, tension headache, sinus headache

In this study, patients were allowed to self-administer lanadelumab after receiving instructions and demonstrating adequate technique. A total of 165 (78%) of subjects (79 non-rollover and 86 rollover) self-administered at least one dose of lanadelumab. With regard to the impact of self-administration on the incidence of injection site reactions, there was no apparent difference in frequency based on administration type (self-administration at home or in clinic, or by study staff). As in study 03, injection site pain, erythema, and bruising were the main types of injection site reactions reported in the OLE.

## Laboratory Findings

### Liver function tests

As in trial 03, LFT elevations were observed in the OLE. The table and figure below show the maximum ALT, AST, and total bilirubin elevation by cohort. In total, there were nine unique subjects with elevated AST and/or ALT and one subject with elevated total bilirubin. No Hy's law cases were identified. Two patients prematurely discontinued treatment due to transaminase elevation as noted above. Most transaminase elevations decreased without intervention or discontinuation of lanadelumab.

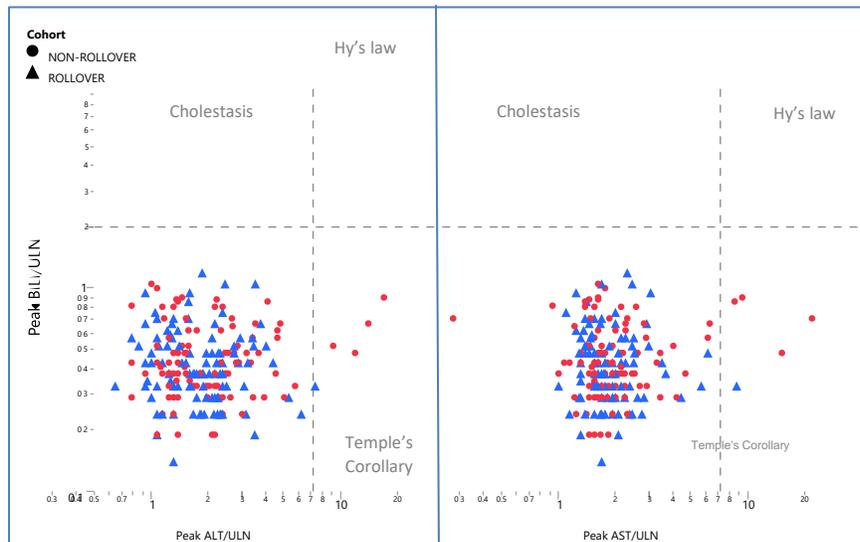
**Table 48. Maximum LFT elevations: DX-2930-04**

Lab parameter (maximum elevation)	Non-rollover (N=103) n (%)	Rollover (N=109) n (%)	Total (N=212) n (%)
<b>ALT</b>			
>3x to ≤5x ULN	1 (1)	2 (2)	3 (1)
>5x to ≤8x ULN	3 (3)	0	3 (1)
>8x to ≤10x ULN	0	0	0
>10x to ≤20x ULN	1 (1)	0	1 (<1)
<b>AST</b>			
>3x to ≤5x ULN	2 (2)	2 (2)	4 (2)
>5x to ≤8x ULN	1 (1)	0	1 (<1)
>8x to ≤10x ULN	1 (1)	0	1 (<1)

Lab parameter (maximum elevation)	Non-rollover (N=103) n (%)	Rollover (N=109) n (%)	Total (N=212) n (%)
<b>Total Bilirubin</b>			
>2x ULN	1 (1)	0	1 (<1)
<b>Total subjects</b>	7 (7)	2 (2)	9 (5)

Source: Reviewer generated table using JMP Clinical  
ULN=upper limit of normal

Figure 44. Hy's law plot: DX-2930-04



Source: Reviewer generated scatter plot in JMP Clinical

### Coagulation tests

In the OLE, a total of six patients (3 rollover, 3 non-rollover) had post-treatment aPTT elevations >1.5x ULN. All had normal aPTT at baseline. Three patients had INR values >2x ULN (1 rollover, 2 non-rollover); one of the non-rollover patients had high INR at baseline. None of the abnormal coagulation tests were associated with bleeding events.

### Immunogenicity

The prevalence of ADA in the OLE was 9% (20/212) and similar to trial 03. The ADA response was transient in 8 of the 20 subjects. Six subjects (3 rollover, 3 non-rollover) had neutralizing ADA. As in the controlled study, the presence of ADA had no apparent impact on PK/PD, efficacy, or safety.

### 8.2.8. Additional Safety Explorations

#### Human Carcinogenicity or Tumor Development

One subject reported an SAE of gluteal fibrosarcoma; however, as this was a relapse of a pre-existing malignancy, this was not felt to be related to lanadelumab treatment. The subject

continued on lanadelumab and underwent surgical resection of the fibrosarcoma. While rare events such as malignancy are unlikely to appear in a clinical development program of this size, lanadelumab is not anticipated to have immunomodulatory effects.

### **Human Reproduction and Pregnancy**

A total of three pregnancies were reported in the development program, all during the OLE. All three subjects were rollover subjects from trial 03 and discontinued treatment following a positive pregnancy test. Two subjects had been exposed to lanadelumab for over a year (Subjects DX-2930-03- (b) (6) and DX2930-03- (b) (6) both on 150 Q4W in trial 03) and one subject had been exposed for approximately 6 months (subject DX-2930-03- (b) (6) on 300 Q4W in trial 03). There were no reported complications during pregnancy. Two of the three women (03- (b) (6) and 03- (b) (6) delivered healthy infants with the third (03- (b) (6) expected to deliver twins after the safety update cutoff.

Refer to Section 5.5.4 for a summary of the nonclinical reproductive studies.

*Reviewer comment: The development program undertook standard precautionary measures to limit the incidence of pregnancy during clinical trials. While the nonclinical data and limited clinical experience are reassuring, no conclusions can be made regarding the impact of lanadelumab treatment on pregnancy.*

### **Pediatrics and Assessment of Effects on Growth**

Safety in adolescent patients 12 to 17 years of age enrolled in trial 03 and OLE study 04 was similar to the safety profile in adults. Lanadelumab is not expected to impact growth. While the consequences of long-term suppression of plasma kallikrein are not fully known, the fact that congenital deficiency of prekallikrein is largely asymptomatic is reassuring. Refer to Section 10 for additional discussion of pediatric issues pertaining to lanadelumab.

### **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Based on the mechanism of action, lanadelumab is not expected to have the potential for drug abuse or dependence. While not a formal study to assess the potential for withdrawal or rebound, results from the OLE 'dose and wait' period do not reveal any concerns for withdrawal or rebound effects.

#### **8.2.9. Safety in the Postmarket Setting**

##### **Safety Concerns Identified Through Postmarket Experience**

There is no postmarketing experience with lanadelumab.

##### **Expectations on Safety in the Postmarket Setting**

Since phase 3 trials excluded patients with certain co-morbidities, such as some pre-existing LFT

abnormalities as well as patients who could not discontinue other long-term prophylaxis or be managed with on-demand therapy alone, it is possible that HAE patients with underlying hepatic dysfunction or more severe disease may experience side effects not observed in clinical trials. Because hypersensitivity reactions were observed in clinical trials, it is possible that more severe hypersensitivity reactions, including anaphylaxis, may occur in the postmarketing setting as more patients are exposed for a longer period of time. However, given the relatively safe profile of lanadelumab, no substantial differences are anticipated.

#### 8.2.10. Integrated Assessment of Safety

The safety data submitted with the BLA was sufficient to assess the safety of lanadelumab in the proposed HAE population. The safety information for lanadelumab is primarily derived from the pivotal, placebo-controlled phase 3 trial DX-2930-03. Additional support for long-term safety comes from OLE study DX-2930-04. Trial 03 included 125 adult and adolescent HAE patients, 84 of whom received at least one dose of lanadelumab and of these 27 received the proposed recommended starting dose of 300 mg Q2W. A total of 212 patients (109 rollover patients from trial 03 and 103 non-rollover patients) received open-label lanadelumab 300 mg Q2W in the OLE study 04.

No deaths occurred in development program. SAEs were single events that appeared unrelated to lanadelumab treatment. TEAEs leading to premature treatment discontinuation were rare and less frequent in lanadelumab treatment arms compared to placebo in trial 03. Safety analyses were performed for AESIs identified *a priori* and potential safety signals identified during the review. Hypersensitivity reactions were reported in a few patients, but symptoms were primarily localized to the injection site and/or self-limited. No cases of anaphylaxis or recurrent hypersensitivity reactions were identified. Injection site reactions (mainly pain, bruising, erythema) occurred frequently in roughly half of lanadelumab-treated patients; however, the frequency was not dose-dependent and the reactions were not dose-limiting. While minor prolongations in aPTT coagulation tests were noted in the lanadelumab treatment arms, there were no reports of adverse events related to bleeding or hypercoagulability in trial 03. Transaminase elevations emerged as a potential safety signal. TEAEs related to increased AST and/or ALT, some of which led to discontinuation, were reported with lanadelumab treatment in the controlled and OLE studies. No potential Hy's law cases were identified in the program. A total of five patients had maximum AST/ALT elevations >3x ULN, all in the lanadelumab treatment arms. However, transaminase elevations were generally transient, asymptomatic, not dose-dependent, and in some cases confounded by underlying co-morbidities. In general, safety data from OLE study 04 was consistent with the placebo controlled data and supports chronic lanadelumab use. Overall, the lanadelumab safety profile for the treatment of a rare, serious disease such as HAE is favorable.

## SUMMARY AND CONCLUSIONS

### 8.3. Statistical Issues

Statistical issues were 1) use of a single study to provide evidence, 2) the lack of use of the data collected post study drug discontinuation in the appropriate analyses, and 3) inconsistency and lack of robustness in how the PRO measures were pre-specified and analyzed in comparison to the other efficacy parameters.

Regarding use of a single study to provide evidence, the persuasive efficacy results (large effect size, low p-value, evidence from multiple doses, evidence from secondary endpoints) are reasons why there is substantial evidence despite the presence of only a single phase 3 study.

The DX-2930-03 individual stopping rules as defined in the protocol were for patients discontinuing study drug to continue the study through completion of all scheduled visits. The SAP description of time to first HAE attack and tipping point analysis does not distinguish between treatment discontinuation and study discontinuation. Data collected from patients who discontinued study drug but remained in the study were apparently not included in these or other analyses. Use of the patient's own data post study drug discontinuation provides the HCP and patient a treatment policy estimand, giving more analytic clarity on what patients who take a drug experience when it is working and also when they need to discontinue drug.

That being said, the study results were very robust in the tipping point analysis due to large active treatment group differences from placebo and relatively little missing data, so this issue did not have an appreciable impact on data interpretation and conclusions.

(b) (4)



### 8.4. Conclusions and Recommendations

The recommended regulatory action from both the clinical and statistical perspective is Approval. The lanadelumab development program for HAE prophylaxis consisted of a single pivotal efficacy and safety trial, DX2930-03 that was adequately conducted and well-controlled. Results from this trial demonstrated substantial evidence of efficacy with all lanadelumab doses compared to placebo in patients with Type I or II HAE for the primary endpoint of monthly attack rate and for multiple supportive endpoints such as rate of moderate-severe attacks, rate

of attacks requiring rescue medication, and proportion of attack-free subjects. Although the numerically greater treatment effect in the high dose arm supports a recommended starting dose of 300 mg Q2W, our review has concluded that the totality of data support providing an option in labeling to extend the dosing interval in some patients from every 2 to every 4 weeks after a period of (b) (4) 6 months to allow flexibility and individualization in dosing while maintaining similar efficacy.

The safety data submitted with the BLA were sufficient to assess the safety of lanadelumab in the proposed HAE population. Hypersensitivity reactions and abnormal bleeding/hypercoagulability events were identified as AESIs *a priori*. No cases of anaphylaxis were identified and hypersensitivity reactions were mild and self-limited. No events related to disordered coagulation were reported. Transaminase elevations emerged as a potential safety signal; however, increases in AST/ALT were generally transient, asymptomatic, not dose-dependent, and in some cases confounded by underlying co-morbidities. Injection site reactions (mainly pain, bruising, erythema) were common, occurring in approximately half of lanadelumab-treated patients; however, the frequency was not dose-dependent or dose-limiting. In general, safety data from OLE study 04 was consistent with the placebo controlled data and supports chronic lanadelumab use. Efficacy and safety results across various demographic and baseline characteristic subgroups were generally consistent with the overall findings. Overall, the risk/benefit profile for lanadelumab in the treatment of a rare, serious disease such as HAE is favorable.

X Susan Duke

Primary Statistical Reviewer

X Yongman Kim

Statistical Team Leader

X Gregory Levin

Associate Director, Division of Biometrics II

X Stacy Chin

Primary Clinical Reviewer and Cross-Disciplinary Team Leader

(e-signatures located on the last page)

## 9 Advisory Committee Meeting and Other External Consultations

A pulmonary allergy drug advisory committee (PADAC) meeting was considered for this application. However, given the results of the studies submitted, the Division decided that the evidence supporting approval for the indicated population was sufficiently robust that discussion at an AC was not necessary.

## 10 Pediatrics

The clinical development program for lanadelumab included ten adolescent HAE patients ages 12 to 17 years in the pivotal trial DX2930-03 and an additional thirteen adolescent patients in the OLE study DX2930-04 (total N=23). The efficacy and safety of lanadelumab for the prophylaxis of HAE attacks in adolescents was similar to adult HAE patients; therefore, this review recommends approval of lanadelumab for HAE patients 12 years of age and older. In addition, the Applicant separately submitted a PPSR for pediatric HAE patients 2 to 11 years of age. (b) (4)

## 11 Labeling Recommendations

### 11.1 Prescription Drug Labeling

The Applicant submitted proposed prescribing information, patient package insert, instructions for use and carton and container labeling for lanadelumab that included the tradename “Takhzyro”, and the suffix -flyo. The label was reviewed by the appropriate disciplines within the Division and labeling consultants who recommended various changes to correct formatting errors and to better describe the drug product and indicated population to healthcare providers and fully inform patients. A high-level summary of significant labeling changes is provided in the table below.

Summary of Significant Labeling Changes		
Section	Proposed Labeling	Approved Labeling
Indications and Usage	Prophylaxis to prevent attacks (b) (4)	Prophylaxis to prevent attacks
Dosage	(b) (4)	Recommended starting dose 300 mg Q2W. Q4W dosing interval is also effective and

BLA 761090 Multi-disciplinary Review and Evaluation  
Takhzyro (lanadelumab)

	(b) (4)	may be considered in patients who are well-controlled patients (e.g., attack-free) for over 6 months
Dosage Form and Strengths	(b) (4) 300 mg/mL	300 mg/mL
Adverse Reactions	Safety exposure from (b) (4)	Safety exposure from controlled study
	Adverse reactions table (b) (4)	Adverse reactions table included all TEAEs occurring ≥10% than placebo
		Added section on transaminase elevations
		Added section on less common adverse reactions
Drug interactions	(b) (4)	Rephrased to state that prolonged aPTT is expected based on MOA and included coagulation test results and (b) (4)
Use in Specific Populations		refer to Section 5.7
Nonclinical toxicology		refer to Section 5.7
Clinical studies	(b) (4)	(b) (4)
	(b) (4)	From the OLE, only included data from dose and wait period in the OLE from the 300 mg Q2W cohort to support extending dosing interval to Q4W after 6 months

DMPP and OPDP reviewed the proposed patient package insert (PPI) and instructions for use (IFU) submitted to the BLA. Revisions to reduce redundancy, make patient information more consistent with the PI and concise were conveyed to and accepted by the Applicant.

## 12 Risk Evaluation and Mitigation Strategies (REMS)

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Given the favorable safety profile of this drug, no additional risk management strategies beyond labeling and routine postmarketing pharmacovigilance are required.

## 13 Postmarketing Requirements and Commitment

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Agreed upon postmarketing commitments include the following:

*PMC #1 – Results from open-label extension study DX-2930-04. Agreed upon final study report submission date: May 2020*

*PMC #2 – Results from a low endotoxin recovery (LER) study using an appropriate container to hold (b) (4) spiked with either RSE or CSE (5-10 EU/mL) at (b) (4) C for (b) (4). Agreed upon final study report submission date: September 208*

PREA requirements do not apply to this orphan drug product; (b) (4)

## 14 Appendices

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### 14.1. Financial Disclosure

The financial disclosure checklist for the main clinical studies submitted to this BLA is provided below. Although there were several significant payments of other sorts, these were unlikely to have had a significant impact upon the conduct of the clinical trials, given that each investigator site enrolled a small number of patients and the efficacy study was randomized, double-blinded, and placebo-controlled with an objective endpoint.

**Covered Clinical Study (Name and/or Number): DX-2930-03 and DX-2930-04**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 35 PIs and 284 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

BLA 761090 Multi-disciplinary Review and Evaluation  
Takhzyro (Ivanadelumab)

<u>18 (14 PIs, 4 sub-investigators)</u>		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>18</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

## 15 Division Director (DPARP)

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This BLA provides for lanadelumab as a prophylaxis to prevent attacks (b) (4) in patients with HAE. HAE is a rare disease with variable attacks of swelling/edema that can potentially be life threatening. In patients with HAE, deficient or dysfunctional C1-INH leads to increased kallikrein activity and release of bradykinin which leads to the characteristic swelling of acute HAE attacks. Lanadelumab is a new fully human IgG1 monoclonal antibody that binds and inhibits plasma kallikrein.

The efficacy and safety of lanadelumab were evaluated in a single, 24-week, adequate and well-controlled, clinical trial in HAE patients 12 years of age and older. Three dosing regimens of lanadelumab were compared to placebo in this clinical trial – 150 mg Q 4 weeks, 300 mg Q 4 weeks, and 300 mg Q 2 weeks. Results from the pivotal trial showed that all dosing regimens of lanadelumab resulted in statistically significant and clinically meaningful reductions in monthly HAE attack rate, monthly rate of moderate to severe HAE attacks, and monthly rate of HAE attacks requiring acute rescue therapy compared to placebo. Secondary endpoints further supported the efficacy of lanadelumab. The recommended starting dose of 300 mg Q2 weeks is supported by a numerically greater treatment effect with this dosing regimen. As described in the clinical pharmacology and statistics section, the data also support providing an option to extend the dosing interval in some patients from 300 mg every 2 weeks to 300 mg every 4 weeks after a period of (b) (4) 6 months without substantial loss of efficacy. This dosing option provides some flexibility for healthcare providers and patients, which is beneficial given the variable nature of HAE.

The safety data showed that injection site reactions were the most commonly reported adverse events. Hypersensitivity reactions and transaminase elevations were also identified as a potential safety signals. However, hypersensitivity reactions were mild and self-limited, and increases in AST/ALT were generally transient, asymptomatic, not dose-dependent, and/or confounded by underlying co-morbidities. These adverse events are described in the product labeling.

Overall, the submitted data support a favorable benefit risk profile for lanadelumab for the treatment of HAE. All disciplines recommend approval and I agree with approval of this application. Lanadelumab provides a new treatment option for patients with HAE and allows for less frequent administration than currently available treatment options. Labeling has been agreed to by the FDA and Applicant. The Applicant has agreed to two post-marketing commitments. (b) (4)

X Sally Seymour  
Division Director

X Mary Thanh Hai  
ODE II Director

BLA 761090 Multi-disciplinary Review and Evaluation  
Takhzyro (lanadelumab)

(e-signatures located at the end)

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BLA 761090 Multi-disciplinary Review and Evaluation  
Takhzyro (lanadelumab)

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BLA 761090, Lanadelumab (TAKHZYRO) uni-review signature page

Pharmacology/Toxicology

**Timothy W. Robison -S** Digitally signed by Timothy W. Robison -S  
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Signing for Matthew Whittaker and Timothy W. Robison

**Timothy J. MCGovern -S** Digitally signed by Timothy J. MCGovern -S  
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Office of Clinical Pharmacology

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**Yongman Kim -S** Digitally signed by Yongman Kim -S  
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/s/  
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STACY J CHIN  
08/23/2018

SALLY M SEYMOUR  
08/23/2018

MARY T THANH HAI  
08/23/2018



**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE: August 17, 2018**

**TO: BLA 761090**

**FROM: Sally Seymour, MD**

**SUBJECT: Division Director Review**

**APPLICATION/DRUG: BLA 761090 (Lanadelumab)**

**Executive Summary**

This BLA provides for lanadelumab as a prophylaxis to prevent attacks (b) (4) in patients with hereditary angioedema (HAE). HAE is a rare disease with variable attacks of swelling/edema that can potentially be life threatening. In patients with HAE, deficient or dysfunctional C1-INH leads to increased kallikrein activity and release of bradykinin which leads to the characteristic swelling of acute HAE attacks. Lanadelumab is a new fully human IgG1 monoclonal antibody that binds and inhibits plasma kallikrein.

The efficacy and safety of lanadelumab were evaluated in a single, 24 week, adequate and well-controlled, clinical trial in HAE patients 12 years of age and older. Three dosing regimens of lanadelumab were compared to placebo in this clinical trial – 150 mg Q 4 weeks, 300 mg Q 4 weeks, and 300 mg Q 2 weeks. Results from the pivotal trial showed that all dosing regimens of lanadelumab resulted in statistically significant and clinically meaningful reductions in monthly HAE attack rate, monthly rate of moderate to severe HAE attacks, and monthly rate of HAE attacks requiring acute rescue therapy compared to placebo. Secondary endpoints further supported the efficacy of lanadelumab. The recommended starting dose of 300 mg Q2 weeks is supported by a numerically greater treatment effect with this dosing regimen. As described in the clinical pharmacology and statistics sections, the data also support providing an option to extend the dosing interval in some patients from 300 mg every 2 weeks to 300 mg every 4 weeks after a period of (b) (4) 6 months without substantial loss of efficacy. This dosing option provides some flexibility for healthcare providers and patients, which is beneficial given the variable nature of HAE.

The safety data showed that injection site reactions were the most commonly reported adverse events. Hypersensitivity reactions and transaminase elevations were also identified as a potential safety signals. However, hypersensitivity reactions were mild and self-limited, and increases in AST/ALT were generally transient, asymptomatic, not dose-dependent, and/or confounded by underlying co-morbidities. These adverse events are described in the product labeling.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Drug Evaluation and Research  
Silver Spring, MD 20993

My review is complete and has been added to the Multi-Disciplinary Review and Evaluation. If I must review information that is subsequently added to the administrative record, I will update my part of the Multi-disciplinary Review and Evaluation document accordingly. Overall, the submitted data support a favorable benefit risk profile for lanadelumab for the treatment of HAE. All disciplines recommend approval. I recommend approval of this application. Lanadelumab provides a new treatment option for patients with HAE and allows for less frequent administration than currently available treatment options. Labeling has been agreed to by the FDA and Applicant. The Applicant has agreed to two post-marketing commitments. [REDACTED] (b) (4)

Refer to the Multi-disciplinary Review and Evaluation for additional details.

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SALLY M SEYMOUR  
08/17/2018

**PHARMACOLOGY/TOXICOLOGY REVIEW**  
**Safety Assessment of Extractables and Leachables**

**Date:** May 4, 2018

**BLA number:** 761090

**Sponsor:** Shire

**Drug substance:** Lanadelumab (mAb against plasma kallikrein)

**Indication(s):** Hereditary angioedema

**Route of administration:** Subcutaneous

**Reviewer name:** Matthew Whittaker, Ph.D.

**Division:** Pulmonary, Allergy, and Rheumatology Products (DPARP)

### EXECUTIVE SUMMARY

Shire has adequately identified potential leachable compounds from the stopper of the lanadelumab drug product container closure system. All potential leachables are qualified for safety from the nonclinical perspective.

#### Introduction

Lanadelumab (DX-2930) is a recombinant, fully human IgG1 $\kappa$  monoclonal antibody directed against the human plasma kallikrein (pKal) enzyme. DX-2930 is designed to block the enzymatic function of pKal and prevent its proteolytic conversion of high molecular weight kininogen (HMWK) to bradykinin. It is to be used as a prophylactic treatment (SC administration) for prevention of angioedema attacks in patients with hereditary angioedema (HAE). The sponsor recommends a dose of 300 mg (SC) every 2 weeks.

The lanadelumab drug product is presented as a ready-to-use liquid solution in a single-use vial, stored at 2 – 8° C. It is intended for self-administration or administration by a caregiver. The complete dose (2 ml) of the product is withdrawn from the vial and injected subcutaneously into the abdomen, thigh, or upper arm.

The lanadelumab drug product composition is as follows:

**Table 1. Lanadelumab drug product composition.**

Component	Quantity per 1.0 mL <sup>a</sup>	Function	Quality Standard
Lanadelumab	150 mg	Active substance	In-house Specification
Sodium phosphate dibasic, dihydrate	5.3 mg	(b) (4)	USP-NF/Ph. Eur.
Citric acid monohydrate	4.1 mg		USP-NF/Ph. Eur.
L-Histidine	7.8 mg		USP-NF/Ph. Eur.
Sodium chloride	5.3 mg		USP-NF/Ph. Eur.
Polysorbate 80	0.1 mg		USP-NF/Ph. Eur.
Water for Injection	(b) (4)		USP-NF/Ph. Eur.

USP-NF = The United States Pharmacopeia and The National Formulary

Ph. Eur. = The European Pharmacopoeia

q.s. = Quantity Sufficient

<sup>a</sup> Quantities are nominal based on targets established for drug substance manufacturing

BLA 761090 was submitted on a rolling basis between 10/31/17 – 12/26/17. The review of the nonclinical pharmacology and toxicology data associated with this application is included in the DPARP Uni-Review document. The current review includes an assessment of the toxicity of extractable compounds from the stopper used in the drug product primary packaging.

The product quality components of the BLA were submitted on 11/17/17. The nonclinical review team submitted an Information Request to the sponsor on 12/7/17 to solicit the complete study reports for assessment of extractables and leachables studies conducted with the drug product (DP) primary packaging. The full study report for a controlled extraction study conducted with the rubber stopper used in the DP vial was submitted to the BLA on 12/19/17. Leachables were not quantified in long-term stability studies with the drug product.

The container closure system for lanadelumab consists of the following components:

- (1) Vial (Manufacturer: (b) (4) )
  - (b) (4) 5 ml (for 300 mg dose), (b) (4) glass, clear.
- (2) Stopper (Manufacturer: (b) (4) )
  - 13 mm (b) (4) rubber stopper (b) (4)  
(b) (4)  
(b) (4)
- (3) Crimp seal (Manufacturer: (b) (4) )
  - The aluminum crimp seal for both vial sizes is a 13 mm, flip-off seal with a matte finish on the top and bottom. The seal does not come in contact with the vial contents at any time.

***Extractables Study***

(b) (4)



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MATTHEW T WHITTAKER  
05/14/2018

TIMOTHY W ROBISON  
05/14/2018  
I concur