



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for Lanadelumab

Proprietary Product Name: Takhzyro

Sponsor: Shire Australia Pty. Ltd.

**March 2020**

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## Common abbreviations

| Abbreviation    | Meaning   |
|-----------------|---|
| ADA             | Antidrug antibody   |
| ADCC            | Antibody dependent cell mediated cytotoxicity   |
| AE              | Adverse event   |
| AE-QoL          | Angioedema Quality of Life questionnaire  |
| AESI            | Adverse event of special interest   |
| ALP             | Alkaline phosphatase  |
| ALT             | Alanine aminotransferase  |
| aPPT            | Activated partial thromboplastin time   |
| ASCIA           | Australasian Society of Clinical Immunology and Allergy   |
| AST             | Aspartate aminotransferase  |
| AUC             | Area under the plasma concentration-time curve  |
| $AUC_{0-HAE}$   | From the first open-label dose to the time of first hereditary angioedema attack in rollover subjects |
| $AUC_{\tau,ss}$ | AUC over the dosing interval at steady state  |
| BMI             | Body mass index   |
| BP              | Blood pressure  |
| C1-INH          | C1 (esterase) inhibitor   |
| $C_{ave,ss}$    | Average concentration at steady state   |
| CDC             | Complement dependent cytotoxicity   |
| CHO             | Chinese hamster ovary   |
| CL/F            | Apparent total plasma clearance after extravascular administration                                    |
| $C_{max}$       | Maximum observed plasma concentration   |

| Abbreviation  | Meaning  |
|---------------|--|
| $C_{\max,ss}$ | Maximum observed plasma concentration at steady state                    |
| CSR           | Clinical study report  |
| DX-2930       | Lanadelumab (drug development code name; also known as SHP643)           |
| $EAUC_{50}$   | Effective area under the curve associated with 50% of the maximum effect |
| ECG           | Electrocardiogram  |
| eCRF          | Electronic case report form  |
| eGFR          | Estimated glomerular filtration rate                                     |
| EMA           | European medicines agency (EU)   |
| $E_{\max}$    | Maximum effect   |
| EQ-5D-5L      | EuroQol Group 5-Dimension-5 Level questionnaire                          |
| EU            | European Union   |
| FDA           | Food and Drug Administration (USA)                                       |
| GI            | Gastrointestinal   |
| HAARP         | Hereditary angioedema attack assessment and reporting procedures         |
| HAE           | Hereditary angioedema  |
| HAWK          | Hereditary Angioedema International Working Group                        |
| HMWK          | High molecular weight kininogen  |
| HRQoL         | Health-related quality of life   |
| $IC_{50}$     | Half maximal (50%) inhibitory concentration                              |
| ICH           | International Council for Harmonisation                                  |
| IgG1          | Immunoglobulin G1  |
| IP            | Intraperitoneal  |

| Abbreviation | Meaning   |
|--------------|---|
| INR          | International normalized ratio  |
| ISR          | Injection site reaction   |
| ISS          | Integrated summary of safety  |
| ITT          | Intent to treat   |
| IV           | Intravenous   |
| LTP          | Long term prophylaxis   |
| mAb          | Monoclonal antibody(ies)  |
| MCID         | Minimal clinically important difference                                 |
| NAFLD        | Non-alcoholic fatty liver disease                                       |
| NBA          | National Blood Authority  |
| NCA          | Noncompartmental analyses   |
| OLE          | Open label extension  |
| pd           | Plasma derived  |
| PK           | Pharmacokinetic(s)  |
| pKal         | Plasma kallikrein   |
| PRO          | Patient-reported outcome  |
| PT           | Preferred Term  |
| Q2W          | Every 2 weeks   |
| Q4W          | Every 4 weeks   |
| QoL          | Quality of life   |
| QTcB         | QT interval, corrected for heart rate according to Bazett's formula     |
| QTcF         | QT interval, corrected for heart rate according to Fridericia's formula |
| SAE          | Serious adverse event   |

| Abbreviation      | Meaning   |
|-------------------|---|
| SC                | Subcutaneous  |
| SD                | Standard deviation  |
| SHP643            | Lanadelumab (drug development code name; also known as DX-2930) |
| SMQ               | Standardized MedDRA Queries                                     |
| SOC               | System Organ Class  |
| TEAE              | Treatment emergent adverse event                                |
| TGA               | Therapeutic goods administration                                |
| T <sub>max</sub>  | Time to reach maximum observed concentration                    |
| ULN               | Upper limit of normal   |
| US                | United States   |
| V <sub>c</sub> /F | Apparent volume of distribution                                 |
| WAO               | World Allergy Organization                                      |



## I. Introduction to product submission

### Submission details

|                                    |  |
|------------------------------------|--|
| <i>Type of submission:</i>         | New biological entity  |
| <i>Decision:</i>                   | Approved   |
| <i>Date of decision:</i>           | 24 January 2019  |
| <i>Date of entry onto ARTG:</i>    | 30 January 2019  |
| <i>ARTG number:</i>                | 302300   |
| <i>, Black Triangle Scheme</i>     | Yes<br>This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia   |
| <i>Active ingredient:</i>          | Lanadelumab  |
| <i>Product name:</i>               | Takhzyro   |
| <i>Sponsor's name and address:</i> | Shire Australia Pty. Ltd.<br>Level 39, 225 George St.<br>Sydney NSW 2000   |
| <i>Dose form:</i>                  | Solution for injection   |
| <i>Strength:</i>                   | 300 mg in 2 mL   |
| <i>Container:</i>                  | Vial   |
| <i>Pack size:</i>                  | Single vial  |
| <i>Approved therapeutic use:</i>   | <i>Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) in patients aged 12 years and older.</i> |
| <i>Route of administration:</i>    | Subcutaneous injection   |
| <i>Dosage:</i>                     | 300 mg every 2 weeks, see Product Information for details.   |

## Product background

This AusPAR describes the application by Shire Australia Pty Ltd (the sponsor) to register Takhzyro lanadelumab 300 mg/2 mL solution for injection for the following indication:

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

Hereditary angioedema (HAE) is a rare life-threatening disorder characterised by recurrent episodes of angioedema that is, the swelling of the subcutaneous tissues due to increased vascular permeability and extravasation of intravascular fluid. Affected individuals have either deficient or dysfunctional C1 esterase inhibitor (C1-INH) protein. C1-INH inhibits the serine proteases Factor XIIa and plasma kallikrein (pKal), regulating the intrinsic pathway of coagulation. FXIIa triggers fibrin formation through activation of Factor XI and also liberates bradykinin from high molecular weight kininogen (HMWK) through cleavage by pKal. Bradykinin mediates the increased vascular permeability. Lanadelumab is a monoclonal antibody (mAb) which targets active pKal preventing the release of bradykinin and the consequent angioedema.

Lanadelumab is the first monoclonal antibody developed for the prevention of HAE. Cinryze (approved for the treatment and prevention of HAE by the TGA on 4 April 2012) and Berinert (approved for the treatment of HAE by the TGA on 5 July 2017) are C1 esterase inhibitors (C1-INH) purified from human plasma. Firazyr (icatibant), a synthetic decapeptide antagonist of bradykinin, was approved for the treatment of HAE by the TGA on 3 September 2010. Kalbitor (ecallantide) is a 60 amino acid recombinant protein inhibitor of (pKal) but is not registered in Australia.

The sponsor requested Priority Review designation for the application to register lanadelumab as a new biological entity which was determined to be a priority applicant by the TGA on 21 February 2018. Lanadelumab also received Orphan Drug designation from the TGA for the same indication on 21 February 2018.

## Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 30 January 2019.

At the time the TGA considered this application; a similar application had been approved or was under consideration in the countries or regions as outlined Table 1.

**Table 1: Overseas regulatory status**

| Country / region | Dates   | Indications  | Other relevant information   |
|------------------|---|--|--|
| USA              | Submitted: 26 December 2017<br>Approved: 23 August 2018 | <i>Takhzyro is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.</i> | Orphan Drug Designation (granted: 26 November 2013)<br><br>Fast Track Designation (granted: 11 March 2015)<br><br>Breakthrough Therapy Designation |

| Country / region           | Dates  | Indications   | Other relevant information  |
|----------------------------|--|---|---|
|                            |  |   | (granted: 2 July 2015)<br><br>Priority Review (granted: March 2018)   |
| Canada                     | Submitted: 22 February 2018<br>Approved: 19 September 2018                 | <i>Takhzyro (lanadelumab injection) is indicated for routine prevention of attacks of hereditary angioedema (HAE) in adolescents and adults.</i><br><br><i>Takhzyro is not intended for acute treatment of HAE attacks.</i> | Priority Review (granted: 6 February 2018)  |
| EU (Centralised Procedure) | Submitted: 8 March 2018<br>CHMP positive opinion received: 18 October 2018 | <i>Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.</i>  | Orphan Drug Designation (granted: 9 October 2015)<br><br>Accelerated Assessment (granted: 22 February 2018) |
| Switzerland                | 6 April 2018<br><br>Decision Pending                                       |   | Orphan Drug Designation (granted: 20 December 2017)   |

## II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

**Table 2: Timeline for Submission PM-2018-01464-1-2**

| Description  | Date             |
|--|------------------|
| Positive Designation (Orphan or Provisional if applicable)       | 21 February 2018 |
| Submission dossier accepted and first round evaluation commenced | 25 May 2018      |

| Description  | Date             |
|--|------------------|
| Evaluation completed   | 23 October 2018  |
| Delegate's Overall benefit-risk assessment and request for Advisory Committee advice | 5 November 2018  |
| Sponsor's pre-Advisory Committee response  | 20 November 2018 |
| Advisory Committee meeting   | 6 December 2018  |
| Registration decision (Outcome)  | 24 January 2019  |
| Completion of administrative activities and registration on ARTG                     | 30 January 2019  |
| Number of working days from submission dossier acceptance to registration decision*  | 147              |

\*Target timeframe for priority applications is 150 working days from acceptance for evaluation to the decision.

### III. Quality findings

#### Introduction

Active plasma kallikrein (pKal) was identified as a suitable therapeutic target in HAE types I and II. Lanadelumab was then discovered by screening an antibody phage display library against active pKal. Lanadelumab binds to pKal such that it occludes the active site and inhibits proteolysis of the endogenous substrate, high molecular weight kininogen (HMWK).

The intent of formulation development was to identify a liquid formulation matrix that stabilizes lanadelumab and is suitable for subcutaneous injection. The final formulation matrix was comprised of buffering agents (sodium phosphate dibasic dihydrate and citric acid), stabilizer (histidine), tonicifier (sodium chloride), and surfactant.

#### Drug substance

Lanadelumab is a recombinant human immunoglobulin G1 (IgG1) kappa mAb that consists of two light chains and two heavy chains. Based on the amino acid sequence, the molecular weight of the non-glycosylated lanadelumab is 145,716 Da.

There was change in the contract manufacturer responsible for supplying drug substance and drug product during the clinical development programme, to allow for Phase III clinical and commercial scale manufacturing. A comparability assessment was performed evaluating the manufacturing process differences between drug substance and product manufactured at the two sites. The comparability assessment supports the statement in the sponsor's Pharmaceutical Development document that 'The only difference in the drug product formulation from Phase I clinical supply to Phase III and commercial drug product is an increase in protein concentration from 100 mg/mL to 150 mg/mL.'

**Table 3: Chemical properties of lanadelumab**

| Property              |   |
|-----------------------|---|
| Composition           | Lanadelumab is a recombinant, human, IgG1, kappa light chain, monoclonal antibody expressed in Chinese hamster ovary (CHO) cells. |
| Mass                  | 145,716 Da  |
| Appearance            | Clear to slightly opalescent, colourless to slightly yellow solution  |
| Protein concentration | 150 mg/mL   |
| Formulation buffer    | Sodium phosphate dibasic dihydrate, citric acid monohydrate, histidine, sodium chloride at pH 6.0, with polysorbate 80            |

The manufacturing process uses a recombinant Chinese hamster ovary (CHO) cells grown in suspension culture. The upstream process consists of vial thaw, inoculum expansion, bioreactor production, and harvest operations. Purification is by affinity chromatography and other chromatography steps and includes a low pH viral inactivation step.

## Drug product

The drug product is manufactured by sterile filtration and aseptic filling of the drug substance into vials after thawing, pooling, and mixing, with no additional excipients with two separate container closure configurations: 2 mL (150 mg dosage) and 5 mL (300 mg dosage) vials, respectively.

All analytical procedures are validated. There are no issues pertaining to specifications.

The stability results support the proposed drug product shelf life of 24 months when stored at  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$  for both strengths.

In use stability data have also been submitted. All the available real time data for in-use stability met the current specification for all key quality attributes. The updated stability data support the short term storage out of refrigeration of drug product vials at  $25^{\circ}\text{C}$  for up to 2 weeks.

The available temperature excursion results indicated that 12 months post the temperature excursion (either at  $25^{\circ}\text{C}$  for one month or two weeks, or up to three cycles of freeze/thaw thermal treatment), all the drug product quality attributes remain within the acceptance criteria. As the proposed shelf life of the drug product is 24 months at  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ , and the stability data for the remainder of the shelf life is not available, the evaluator will not recommend temperature excursion conditions for product storage or shipment. The sponsor is recommended to apply for temperature excursion allowance when these stability data is available.

## Quality summary and conclusions

There are no objections on quality grounds to the approval of Takhzyro.

## Proposed conditions of registration

The quality evaluator has recommended the following as a condition of registration:

1. Batch release testing and compliance with Certified Product Details (CPD)
  - a. It is a condition of registration that all batches of Takhzyro imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - b. It is a condition of registration that each batch of Takhzyro imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index>.
  - c. The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact [Biochemistry.Testing@health.gov.au](mailto:Biochemistry.Testing@health.gov.au) for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at <https://www.tga.gov.au/publication/testing-biological-medicines>
  - d. This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

## 2. Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

## IV. Nonclinical findings

### Introduction

The sponsor has applied to register a new biological entity, lanadelumab (Takhzyro). Takhzyro is proposed to be used for the prevention of angioedema attacks and the control of symptoms of HAE in patients aged 12 years and over. The proposed dosing regimen involves subcutaneous administration of 300 mg every 2 weeks.

### General comments

The submitted nonclinical data were in general accordance with the International Conference on Harmonisation (ICH) guideline.<sup>1</sup> All pivotal repeat-dose toxicity and reproductive toxicity studies were Good Laboratory Practice (GLP) compliant. Lanadelumab is the first mAb developed for the treatment of HAE. The development of anti-drug antibodies limited the exposure to lanadelumab in rodent species which precluded the use of these species in pivotal studies.

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<sup>1</sup> ICH harmonised tripartite guideline preclinical safety evaluation of biotechnology-derived pharmaceuticals S6(R1)

## Pharmacology

Hereditary angioedema (HAE) is a rare life-threatening disorder characterised by recurrent episodes of angioedema that is, the swelling of the subcutaneous tissues due to increased vascular permeability and extravasation of intravascular fluid. Affected individuals have a total or functional deficiency of the C1-INH protein. C1-INH inhibits the serine proteases Factor XIIa and pKal, regulating the intrinsic pathway of coagulation. FXIIa triggers fibrin formation through activation of factor XI and also liberates bradykinin from HMWK through cleavage by pKal. Bradykinin mediates the increased vascular permeability. Lanadelumab is a monoclonal antibody which targets active pKal preventing the release of bradykinin and the consequent angioedema.

As there are no preclinical models of HAE available primary pharmacology studies were conducted principally *in vitro*. These studies established an approximate inhibitor constant ( $K_i$ ) for inhibition of human pKal of 0.125 nM (approximately ( $\sim$ ) 2000 times below the clinical maximum observed concentration at steady state ( $C_{max,ss}$ ) of 0.266  $\mu$ M), slightly higher than the  $K_i$  for cynomolgus monkeys (0.069 nM) and slightly lower than the  $K_i$  for rats (0.17 nM), the two species used in the preclinical studies. Indirect evidence of *in vivo* activity was obtained from the demonstration that HMWK cleavage following contact system activation with dextran sulfate or kaolin was inhibited *ex vivo* in plasma taken from cynomolgus monkeys and rats following single subcutaneous (SC) injections of lanadelumab. Evidence of lanadelumab activity *in vivo* was obtained in a rat paw inflammation/oedema model. A single SC or intraperitoneal (IP) dose of lanadelumab at  $\geq 3$  mg/kg inhibited the paw swelling in rats injected with carrageenan, which induces inflammation and oedema that involves multiple mediators including kinins, pro-inflammatory cytokines, histamine, 5-hydroxytryptamine, and prostaglandins.

## Secondary pharmacodynamics and safety pharmacology

Lanadelumab did not inhibit any of 20 non-target serine proteases (including prekallikrein, tissue kallikrein 1/2/5/12 and Factors Xa/XIa/XIIa) at concentrations up to 1  $\mu$ M,  $\sim 4$  times the maximum anticipated clinical  $C_{max,ss}$ . Binding of lanadelumab to purified Fc receptors or C1q was comparable to that for a human IgG pool and other antibodies (including trastuzumab and rituximab) suggesting lanadelumab has low Fc effector function potential. It did not induce antibody dependent cell mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC) at up to 60  $\mu$ g/mL *in vitro*.

No dedicated safety studies were submitted. A functional observational battery was conducted in Weeks 1 and 4 of the 4 week repeat dose study in rats to assess central nervous system (CNS) effects. No effects were observed up to the highest dose (50 mg/kg). Cardiovascular function was assessed in the repeat-dose studies in cynomolgus monkeys. Heart rate was reduced at 19 to 21 h after the last dose in males given 50 mg/kg SC for 4 weeks, but was increased at 23 to 24 h after dosing. This was an isolated observation and no comparable observations were made in the 6 month SC study, or the 4 week IV study at the same dose and exposures and is unlikely to be of toxicological significance. Respiration was monitored by observation in the monkey studies with no effects noted.

## Pharmacokinetics

Lanadelumab was slowly but well absorbed following SC administration. The average time to maximum concentration ( $T_{max}$ ) value following SC administration in rats and monkeys ranged from 2 to 5 days which is comparable to the human estimated value of around 5 days via the SC route. The pharmacokinetics (PK) was linear at 5 to 50 mg/kg in rats and monkeys. No sex differences in plasma kinetics were observed. Typical of monoclonal antibodies, plasma half-life values were long (1.5 to 4.5 days in rats and around 10 days in

monkeys, compared with around 15 days in humans). The bioavailability in monkeys following subcutaneous dosing was 66% (no data for rats).

No studies were performed to investigate the tissue distribution of lanadelumab in non-pregnant animals. The volume of distribution in cynomolgus monkeys ranged from 80 to 100 mL/kg following intravenous administration of 5 to 50 mg/kg. These values are in the range of blood volume data for cynomolgus monkey which is as expected for a mAb. Total systemic clearance of lanadelumab in monkeys following IV dosing was 0.14 mL/h/kg. The volume of distribution (Vd) and clearance (CL/F) in monkeys were comparable to the population estimates in humans (Vd ~ 183 mL/kg and CL/F ~ 0.356 mL/h/kg for a 70 kg person).

No metabolism studies were performed since lanadelumab is a member of a therapeutic class understood to be degraded into smaller peptides and individual amino acids.

The pharmacokinetic profiles in rats and cynomolgus monkeys were sufficiently similar to those in humans (in addition to similar pharmacological activity to rat, monkey and human pKa) to allow them to serve as appropriate models for the assessment of drug toxicity. While anti-drug antibodies prevented the long term dosing in rats, adequate exposures were achieved in the 4 week study in rats. There were relatively few animals with anti-drug antibodies in monkey studies and these did not preclude the generation of quality results in this species.

## **Toxicology**

### **Acute toxicity**

Five acute toxicity studies were submitted. Two studies in cynomolgus monkeys employed a single dose (20 mg/kg SC) and were essentially evaluations of different lanadelumab formulations. In the rat study no toxicity was observed at the maximum dose tested (50 mg/kg SC) but small increases in activated partial thromboplastin time (aPPT) were noted at both doses tested (25 and 50 mg/kg SC). Similar observations were made at the same doses in the repeat-dose study in rats. Drug formulations containing 100 and 150 mg/mL lanadelumab manufactured at two different sites and used in Phase I and Phase III clinical studies, respectively, did not induce observable toxicity in monkeys at 20 mg/kg SC. Similarly, no toxicity was observed in monkeys dosed with two formulations containing 100 or 200 mg/mL lanadelumab at 20 mg/kg SC. Single doses up to 50 mg/kg either SC or by IV infusion were tested in cynomolgus monkeys with no toxicity noted. The only observation was a transient increase in aPPT in males given 50 mg/kg SC. This was not reported in the repeat dose studies in monkeys. Lanadelumab has low acute toxicity by the proposed clinical route.

### **Repeat-dose toxicity**

One 4 week study was conducted in rats but no further studies were conducted in this species. The sponsor provided a valid justification on the basis of the formation of anti-lanadelumab antibodies in this species. Single 4 week and 6 month studies in cynomolgus monkeys were conducted using SC administration and one 4 week study in cynomolgus monkeys was conducted using IV infusion by weekly administration. The species used and the duration of the studies were consistent with ICH guidelines for biopharmaceuticals.

### **Relative exposure**

Exposure ratios have been calculated based on animal: human plasma area under the curve from time zero to 168 h ( $AUC_{0-168\text{ h}}$ ), normalised to the clinical dose regimen of every



2 weeks. Human reference values are from the clinical Study DX-2930-04. The area under the curve (AUC) data used for animals is the mean of the combined male and female values on the last sampling occasion. The repeat dose studies achieved high exposure levels up to 29 times the anticipated clinical exposure.

**Table 4: Relative exposure in repeat dose toxicity studies**

| Species                        | Study duration<br>[Study no.] | Dose<br>(mg/kg/week, SC) | AUC <sub>0-168h</sub> <sup>^</sup><br>(µg.h/mL) | Exposure ratio <sup>#</sup> |
|--------------------------------|-------------------------------|--------------------------|---|-----------------------------|
| <b>Rat (SD)</b>                | 4 weeks<br>[Study R8056M]     | 5                        | 2137.5  | 0.4                         |
|                                |                               | 25                       | 859.5   | 0.15                        |
|                                |                               | 50                       | 3045.5  | 0.5                         |
| <b>Monkey<br/>(cynomolgus)</b> | 4 weeks<br>[Study P8059M]     | 5 [IV]                   | 11570   | 2                           |
|                                |                               | 25 [IV]                  | 53400   | 9                           |
|                                |                               | 50 [IV]                  | 123000  | 22                          |
|                                | 4 weeks<br>[Study P8057M]     | 5                        | 11550   | 2                           |
|                                |                               | 25                       | 61450   | 11                          |
|                                |                               | 50                       | 153000  | 27                          |
|                                | 6 months<br>[Study P8058M]    | 5                        | 10850   | 2                           |
|                                |                               | 25                       | 52300   | 9                           |
|                                |                               | 50                       | 167500  | 29                          |
| <b>Human (HAE patients)</b>    | Steady state [DX-2930-04]     | 300 mg every 2 weeks     | 11376 (AUC <sub>tau,ss</sub> ) <sup>†</sup>     | -                           |

<sup>^</sup> = data are for the sexes combined at the last sampling occasion; <sup>#</sup> animal AUC<sub>0-168h</sub> x 2/human AUC<sub>tau,ss</sub>;

<sup>†</sup> AUC<sub>tau,ss</sub> = 474 µg.d/mL x 24

### Major toxicities

No major toxicities were identified following the administration of lanadelumab. Some disturbance of liver structure was observed in rats; elevated serum enzymes aspartate transaminase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT), increased liver weights and hypertrophy of Kupffer cells. The increased weight and elevated ALT levels persisted through the recovery period in males given the highest dose. Elevated levels of AST were seen in male monkeys given 50 mg/kg in the 4 week SC study but no other effects on the liver were observed in this species and no effects on liver enzymes were seen in the 6 month study in monkeys. Liver toxicity is not expected in patients.

Increases in aPPT were observed in rats at all doses tested (and also in the single dose study) but were not accompanied by abnormal bleeding. Prolonged aPPT was also detected in the single dose monkey study at 50 SC (males only), but not in the repeat dose studies. The prolonged aPPT was a result of the pharmacological activity of lanadelumab. aPPT was also prolonged in cynomolgus monkey and human plasma, and to a lesser extent, rat plasma incubated with lanadelumab *in vitro*.

### Genotoxicity

No genotoxicity studies were submitted based on ICH S6 (R1).<sup>2</sup> In addition, there are no aspects of the structure of lanadelumab to indicate any cause for concern in this respect.

### Carcinogenicity

No carcinogenicity studies were submitted. The sponsor has provided valid justifications on practical and theoretical grounds. The immunogenicity of lanadelumab in rats causes a reduction in systemic exposure which would introduce uncertainty into any negative result. Evidence from a range of published studies suggests that inhibition of pKal and bradykinin production would be more likely to reduce rather than promote the risk of carcinogenesis.

### Reproductive toxicity

Two reproductive studies were conducted in cynomolgus monkeys. The fertility study did not investigate fertility directly but rather relied on indirect measures; measurement of semen/sperm properties in males and menstrual cycles in females and reproductive organs after 13 weeks of weekly dosing. The second study assessed embryofetal development and monitored surviving offspring during the first 3 months of life. Treatment in this study was during gestation only (from gestation Day 20 to delivery).

### Relative exposure

The reproductive toxicity studies achieved high exposure levels up to 28 times the anticipated clinical exposure.

**Table 5: Relative exposure in reproductive toxicity studies**

| Species                         | Study duration<br>[Study no.]                           | Dose<br>(mg/kg/week,<br>SC) | AUC <sub>0-168h</sub> <sup>^</sup><br>(µg.h/mL) | Exposure<br>ratio <sup>#</sup> |
|---------------------------------|---|-----------------------------|---|--------------------------------|
| <b>Monkey<br/>(cynomolgus)</b>  | 13 week fertility<br>[P8060M]                           | 10                          | 27700   | 5                              |
|                                 |   | 50                          | 103000  | 18                             |
|                                 | Embryofetal and<br>postnatal<br>development<br>[P8062M] | 10                          | 28100   | 5                              |
|                                 |   | 50                          | 159000  | 28                             |
| <b>Human (HAE<br/>patients)</b> | Steady state [DX-<br>2930-04]                           | 300 mg Q2W                  | 11376<br>(AUC <sub>tau,ss</sub> ) <sup>†</sup>  | -                              |

<sup>^</sup> = data are for the sexes combined at the last sampling occasion; <sup>#</sup> animal AUC<sub>0-168 h</sub> x 2/human AUC<sub>tau,ss</sub>; <sup>†</sup> AUC<sub>tau,ss</sub> = 474 µg.d/mL x 24

There were no effects of lanadelumab on sperm properties, menstrual cycles or reproductive organs in cynomolgus monkeys.

Distribution to the foetus and milk was demonstrated in monkeys. Fetal plasma concentrations on postnatal Day 7 were 50 to 90% of levels in maternal plasma, while low levels of lanadelumab were detected in milk (< 0.2% of maternal plasma levels). There were no effects on pregnancy, parturition or embryofetal development. There was a small

<sup>2</sup> CPMP/ICH/302/95; ICH Topic S6. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

dose-dependent reduction in weight gain in infants during the post-natal period. The small, uneven numbers in the different groups, however, do not exclude an effect due to chance.

### ***Pregnancy classification***

The sponsor has proposed Pregnancy Category B1.<sup>3</sup> This classification is appropriate.

### **Local tolerance**

Local tolerance was assessed in the repeat-dose toxicity studies. In both the rat and monkey studies there were variable degrees of haemorrhage and inflammation at SC injection sites. These inflammatory changes mostly resolved in 4 weeks following cessation of injections.

### **Tissue cross-reactivity**

Immunohistochemical methods were used to evaluate cross-reactivity of lanadelumab with normal human tissues. Minimal to mild staining of endothelial cells from multiple tissues was observed. In addition, there was positive staining in a variety of central and peripheral nervous tissues, the eye (outer plexiform layer of retina and nerve fibres in the optic disc), colon and small intestine (parasympathetic ganglion cells in Auerbach's plexus). This distribution of binding is consistent the known localisation of kallikrein and/or prekallikrein in vascular endothelial cells and in neuronal cell bodies using rabbit anti-human pKal or pKal C-terminal end of the heavy chain or murine or rabbit anti-human prekallikrein serum<sup>4,5,6</sup>.

In the study by Fink et al (2007);<sup>6</sup> positive staining obtained with an antibody to the pKal C-terminal end of the heavy chain was identical to staining with anti-prekallikrein antibodies that detect both pKal and prekallikrein. It was assumed that the immunohistochemical processing caused contact system activation leading to the comparable staining with pKal specific antibody and anti-prekallikrein antibody. However, it was also possible that both pKal and prekallikrein are present in tissues in physiological conditions. As lanadelumab does not bind to the inactive prekallikrein, it was possible that prekallikrein was converted to the active form pKal in tissue processing or pKal is present in these tissues.

### **Paediatric use**

Lanadelumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

## **Nonclinical summary and conclusions**

- The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines (ICH S6).<sup>2</sup> The overall quality of the non-clinical dossier was good with all pivotal studies conducted according to GLP.

<sup>3</sup> Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

<sup>4</sup> Cerf ME et al. (1999) Plasma kallikrein localisation in human blood vessels. *Immunopharmacology* 44: 75–80

<sup>5</sup> Cerf ME & Raidoo DM (2000) Immunolocalization of plasma kallikrein in human brain. *Metabolic Brain Disease* 15: 315-323

<sup>6</sup> Fink E et al. (2007) Cellular expression of plasma prekallikrein in human tissues. *Biological Chemistry* 388: 957–963

- *In vitro*, lanadelumab inhibited human pK<sub>1</sub> with K<sub>i</sub> value at least three orders of magnitude below the expected clinical plasma concentrations. There are no preclinical models of HAE but indirect evidence of *in vivo* activity was obtained from the demonstration that HMWK cleavage following contact system activation was inhibited *ex vivo* in plasma taken from cynomolgus monkeys and rats following single SC injections of lanadelumab. A single SC or IP dose of lanadelumab inhibited paw swelling in the rat model of inflammation and oedema induced by carrageenan.
- Lanadelumab did not inhibit any of 20 non-target serine proteases (including prekallikrein, tissue kallikrein 1/2/5/12 and Factors Xa/XIa/XIIa) at concentrations up to 1 µM, ~ 4 times the maximum anticipated clinical exposure.
- No dedicated safety studies were submitted. No adverse effects were seen on CNS function (repeat dose study in rats), or cardiovascular or respiratory function in repeat dose studies in cynomolgus monkeys.
- The pharmacokinetic profile in monkeys was qualitatively similar to that of humans. Lanadelumab was slowly absorbed via the SC route with similar T<sub>max</sub> values in monkeys and humans. Half-life values in monkeys were similar to those in humans.
- Lanadelumab showed no toxicity in rats or monkeys following single SC or IV doses up to 50 mg/kg. The only finding was a slight prolongation of aPTT, attributable to the pharmacological activity of lanadelumab.
- Repeat dose toxicity studies by the subcutaneous route were conducted in rats (4 weeks) and cynomolgus monkeys (up to 6 months). A single 4 week study in monkeys employed IV infusion. Maximum exposures (AUC) were low in rats while exposures well in excess of the anticipated human exposures were achieved in monkey studies. No major toxicities were observed in monkeys. Small increases in serum AST, ALP and ALT, increased liver weights and hypertrophy of Kupffer cells were observed in rats, but these are not expected in humans given the absence of effects in monkeys at exposures higher than that in rats.
- No genotoxicity or carcinogenicity studies were submitted, which are acceptable for a mAb.
- Reproductive effects were assessed in cynomolgus monkeys. There were no effects of lanadelumab on sperm properties in males or menstrual cycles in females and reproductive organs. There were no lanadelumab related effects on pregnancy, parturition or embryofetal development.

### Conclusion

- The submitted preclinical data were in general accordance with the ICH guideline on the non-clinical evaluation of biotechnology-derived pharmaceuticals.<sup>2</sup> All pivotal repeat dose toxicity and reproductive toxicity studies were GLP compliant.
- *In vitro*, lanadelumab inhibited human pK<sub>1</sub> without activity to prekallikrein or tissue kallikreins.
- Clinically significant off-target activities are unlikely and no safety concerns were identified.
- No major toxicities were observed in repeat dose studies in rats or cynomolgus monkeys.
- There was no evidence of teratogenicity in primates.
- There are no nonclinical objections to the registration of lanadelumab for the proposed indication.

The nonclinical evaluator also made recommendations relating to the Product Information (PI) and the Risk Management Plan (RMP) but these are beyond the scope of the AusPAR.

## V. Clinical findings

### Introduction

Lanadelumab is a therapeutic mAb. The IgG1, kappa light chain antibody is human and produced in CHO cells using recombinant technology. It is described as '*a potent and specific inhibitor of active plasma kallikrein (pKal) activity that rapidly binds both soluble and membrane bound forms of the enzyme*' and is a first-in-class mAb to kallikrein.

The proposed indication was initially:

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

In response to a question from the evaluator (see below), the sponsor has proposed the revised indication of:

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

Lanadelumab is presented as a ready-to-use, sterile, preservative free solution in a single use glass vial, with each mL containing 150 mg of lanadelumab. There were two proposed dosage sizes: 150 mg in 1 mL and 300 mg in 2 mL<sup>7</sup>

The following recommendations for dose are proposed for the PI:

Takhzyro should be administered subcutaneously. Maximal efficacy was observed at doses of 300 mg every 2 weeks and is the recommended dose. Doses of 300 mg every 4 weeks and 150 mg every 4 weeks have also been studied.

According to the sponsor, these recommendations allow '*flexibility for physicians to select the optimal dosing regimen for their individual patient due to the inherent variability and unpredictability of HAE*'.

The optimal dose and frequency for lanadelumab, and whether this would vary across individuals or across time within an individual, has not been established. As noted in the Clinical Overview, the pivotal study '*was not designed to compare the treatment effect within the 3 randomized lanadelumab treatment arms. Nor was it designed to evaluate clinical treatment strategy of either starting high (300 mg q2wks) or low (150 mg q4wks) and titrating the dose appropriately based on individual response.*'

Subcutaneous administration into the abdomen, thigh, or upper arm by the patient, care giver or healthcare professional is proposed. A brief description of the steps required for administration is provided in the PI with detailed description and accompanying graphics provided in the Consumer Medicine Information (CMI).

Current guidelines emphasize the importance of home administration for greater patient convenience. If self-administration of lanadelumab is approved, it will be important that both training and 'how-to' information in patient-appropriate language is provided. The PI and CMI should also provide appropriate warnings regarding self-administration using wording such as that used in the PIs for parenteral agents currently used in the management of HAE (Berinert, Cinryze and Firazyf).

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<sup>7</sup> Clarification: Only 300 mg in 2 mL is registered

**Information on the condition being treated**

Hereditary angioedema (HAE) is a rare disorder with an estimated incidence of 1 per 10,000 to 1 per 50,000 with no ethnic group differences. Based on registry data, the Australasian Society of Clinical Immunology and Allergy (ASCIA) estimates the prevalence in the Australian population to be 0.18 per 100,000 population.

***Clinical presentation***

Hereditary angioedema usually presents in childhood or adolescence with episodic attacks of non-itching, non-pitting, well-circumscribed areas of subcutaneous or submucosal oedema that primarily involve the extremities, face, upper airway and gastrointestinal tract. The attacks are self-limited, usually peaking at 24 hours and resolving over 2 to 5 days in the absence of treatment. Initiating factors are poorly understood and attacks may occur without any evident precipitant. Recognised attack triggers include trauma (including surgery and dental work), stress, infections and changes in hormonal status (puberty, oral contraceptive pill, pregnancy). Recurrent attacks continue throughout the life of the patient and may vary over time in severity, duration, and location. The frequency of attacks varies greatly both among affected individuals and over time for a given individual, from more than once a week to a year or more between attacks.

The oedema, depending on its location, may carry significant morbidity and mortality. Laryngeal or upper airway oedema may cause fatal asphyxiation. Prior to modern management, approximately 10% of patients underwent a tracheostomy as a result of airway episodes and mortality was 30%. Laryngeal or upper airway oedema is rare and accounts for an estimated 1% of all episodes. However, the lifetime incidence of a laryngeal attack is estimated at 50 to 70%. Oedema of the bowel mucosa is the most frequent clinical manifestation of HAE and may cause nausea, vomiting, abdominal distension and severe pain requiring opioid analgesia and hospitalisation. Unnecessary abdominal surgery, including appendectomy and exploratory laparotomy, may be performed.

***Pathology***

HAE is most commonly inherited as an autosomal dominant trait with a loss-of-function mutation in the SERPING1 gene that codes for the C1-INH plasma protein, resulting in low circulating levels of C1-INH (HAE type I, ~ 85% of HAE) or dysfunctional C1-INH (HAE type II, ~ 15%).

Under normal circumstances, the main function of C1-INH is the inhibition of the complement system to prevent spontaneous activation. C1-INH also inhibits proteases of the fibrinolytic, clotting, kinin pathways and it is the most important physiological inhibitor of pKal.

Localised tissue oedema in HAE attacks is thought to result from uncontrolled production of bradykinin. This small vasoactive peptide acts on bradykinin B2 receptors to increase vascular permeability and to cause vasodilatation of both arteries and veins. Bradykinin is produced by the action of the activated serine protease, pKal, on circulating high molecular weight kininogen. Activated kallikrein (pKal) is produced from circulating prekallikrein by a number of mechanisms, including activation of the complement system. The importance of the plasma kallikrein-kinin pathway and bradykinin in HAE is supported by the effectiveness of the kallikrein inhibitor, ecallantide, and the bradykinin receptor antagonist, icatibant, in the treatment of acute attacks. HAE patients have also been demonstrated to have elevated cleaved HMWK levels both during and between attacks.

HAE with normal C1-INH levels and function (HAE type III) is the least common form of HAE (< 1%). The underlying genetic mutation(s) and pathophysiology are not yet fully understood.



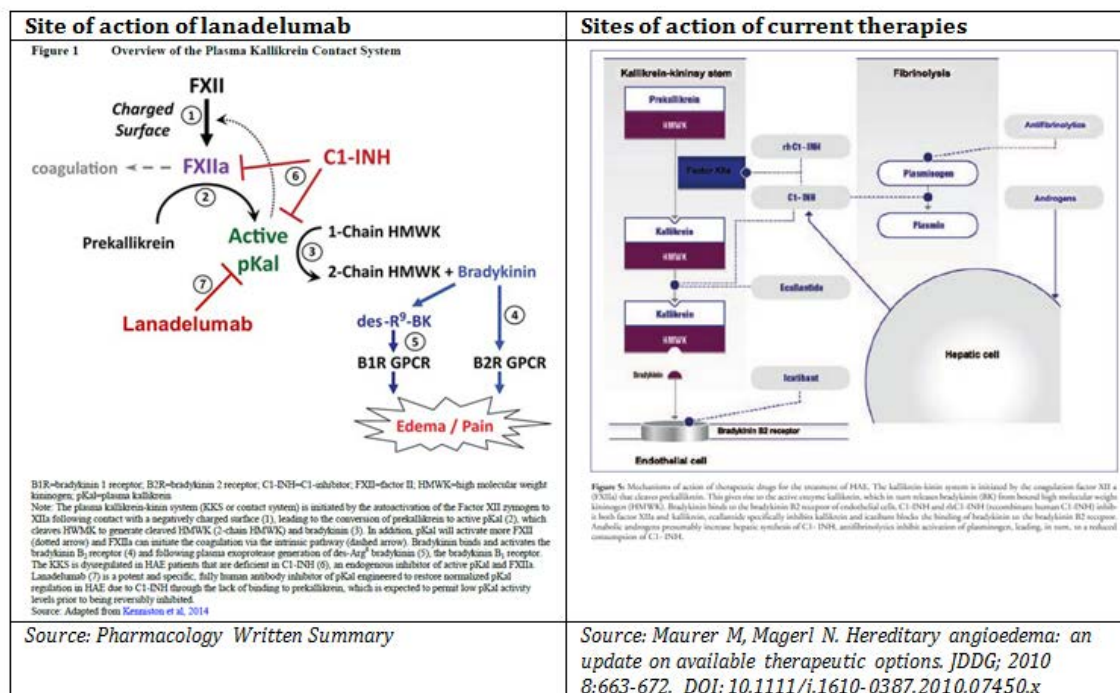
## Diagnosis

Diagnosis of HAE types I and II is by clinical suspicion, based on clinical presentation and positive family history. Abnormalities of C1-INH are determined by serum C1-INH level and functional assays. Serum C4 level may be used as a screening test; in most HAE type I and II patients this is reduced both between and during attacks.

## Current treatment options

Previously treatment options in HAE were limited to attenuated androgens, plasma products (fresh frozen plasma, solvent detergent plasma as sources of C1-INH) and protease inhibitors (anti-fibrinolytic agents such as tranexamic acid and epsilon aminocaproic acid). Treatment options have rapidly expanded in the past decade, with the availability of exogenous C1-INH concentrates (both human plasma derived forms, Cinryze and Berinert, and a recombinant form, conestat alfa); the pKal inhibitor, ecallantide (a polypeptide that binds to the active site of pKal); and the selective competitive bradykinin B2 receptor antagonist, icatibant. These newer treatments are thought to act on different levels of the plasma kallikrein-kinin system. The figure below includes simplified graphics of the plasma kallikrein-kinin system and the sites of drug action.

**Figure 2: Plasma kallikrein-kinin system and sites of action of lanadelumab and current therapies**



## International guidelines

### HAE type I and II (HAE with deficient or dysfunctional C1-INH)

In response to the rapid changes in treatment options, the Hereditary Angioedema International Working Group (HAWK) has produced a sequence of guidelines on the management of HAE based on available evidence and international expert consensus.<sup>8,9,10,11</sup> A similar guideline was produced by the World Allergy Organization

<sup>8</sup> Bowen T, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy, Asthma, and Clinical Immunology : Official Journal of the Canadian Society of Allergy and Clinical Immunology. 2010; 6: 24.

(WAO) in 2012;<sup>12</sup> and updated in 2018.<sup>13</sup> These guidelines divide treatment recommendations according to acute treatment, short term prophylaxis and long term prophylaxis.

The recommended management of acute attacks involving the face, upper airway or abdomen is by the parenteral administration of C1-INH concentrate (plasma derived or recombinant) or ecallantide or icatibant as soon as possible. A response in terms of symptom improvement is expected within 30 min to 2 hours with these treatments. Acute attacks in other body locations may be managed expectantly or by one of these treatments.

Options for short term prophylaxis (that is, to be administered for several days before and after known triggers, such as dental work or surgical procedures) include administration of a C1-INH concentrate or oral attenuated androgen, with C1-INH concentrate currently preferred by the guidelines. With either option, on-demand therapy must also be available due to the varying effectiveness of short term prophylaxis.

With the effectiveness of newer on-demand treatments, two approaches to long term care are accepted, with these being on-demand treatment alone or on-demand treatment plus long term prophylaxis. There are no generally accepted indications for the introduction of long term prophylaxis, although it is generally agreed that it should be considered in severely symptomatic patients who fail to achieve adequate control with appropriate on-demand therapy.<sup>14</sup> Treatment options include C1-INH, attenuated androgens and antifibrinolytics. C1-INH concentrate is currently the preferred first-line option in the guidelines, with androgens second-line. When used for long term prophylaxis, C1-INH is administered intravenously every 3 to 4 days. A formulation for subcutaneous administration (Haegarda), with the same administration frequency, has recently been approved by the US Food and Drug Administration (FDA). Attenuated androgens are administered orally and usually daily. Side effects and drug-drug interactions are common. The use of oral anti-fibrinolytic agents is now rare and tends to be limited to children, due to androgen side effects and difficulties with parenteral therapies in this population.

<sup>9</sup> Bowen T. Hereditary angioedema: beyond international consensus - circa December 2010 - The Canadian Society of Allergy and Clinical Immunology Dr. David McCourtie Lecture. *Allergy, Asthma, and Clinical Immunology : Official Journal of the Canadian Society of Allergy and Clinical Immunology*. 2011; 7: 1.

<sup>10</sup> Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. *Allergy*. 2017; 72: 300-313.

<sup>11</sup> Longhurst H. Optimum Use of Acute Treatments for Hereditary Angioedema: Evidence-Based Expert Consensus. *Frontiers in Medicine*. 2017; 4: 245.

<sup>12</sup> Craig T, Pürsün EA, Bork K, et al. WAO Guideline for the Management of Hereditary Angioedema. *The World Allergy Organization Journal*. 2012; 5: 182-199.

<sup>13</sup> Maurer et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *World Allergy Organization Journal* 2018; 11:5

<sup>14</sup> The WAO guidelines consider various factors that clinicians should consider when evaluating patients for long term prophylaxis (LTP). LTP should be individualized and considered in all severely symptomatic patients with HAE type I/II, taking into consideration; Disease activity; Frequency of attacks; Patient's QoL; Availability of healthcare resources; Failure to achieve adequate control with on-demand therapy; Patient preference



**Table 6: Characteristics of treatment options for long term prophylaxis<sup>11, 13, 15, 16, 17</sup>**

| Treatment option  | Characteristics  |
|---|--|
| Human derived C1-INH concentrate: Cinryze, Berinert             | <ul style="list-style-type: none"> <li>Cinryze has been approved by the TGA for long term prophylaxis; both are approved for acute attacks. The dosing interval is 3 to 4 days for long term prophylaxis.</li> <li>Both require preparation (powder to dissolve) and intravenous administration.</li> <li>Common adverse reactions: nonspecific symptoms, like nausea, vomiting, diarrhoea, and headache.</li> <li>Rare adverse reactions: venous and arterial thrombosis (both); worsening laryngeal oedema and laryngospasm (Berinert); severe hypersensitivity reactions, including anaphylaxis</li> <li>Potential for viral transmission minimised by pasteurisation and nanofiltration.</li> </ul>  |
| Human derived C1-INH concentrate for SC administration Haegarda | <ul style="list-style-type: none"> <li>Not included in guidelines as yet. Approved by the FDA for prophylaxis in June 2017.</li> <li>Requires reconstitution prior to SC administration; dosing interval of 3 to 4 days.</li> <li>Substantial reduction in 'time normalised' HAE attacks: from median 3.8 (placebo) to 0.3 with Haegarda; 40% attack free.</li> <li>Adverse reactions as for IV preparations.</li> </ul>   |
| Attenuated androgens: danazol                                   | <ul style="list-style-type: none"> <li>Only recommended for prophylaxis.</li> <li>Oral administration (daily or twice daily administration).</li> <li>Common adverse reactions include: weight gain, headache, myalgia, depression, and acne (all); virilisation, menstrual disorders, hirsutism, diminished libido (women); premature closure of growth plates, hypogonadism, menstrual irregularities (children and adolescents); virilisation of foetus (pregnant women). Less common adverse reactions include hyperglycaemia, hypertension, abnormal liver enzymes, hepatic necrosis, hepatic carcinoma.</li> <li>Drug-drug interactions common.</li> <li>6 monthly monitoring for adverse effects, including blood tests and 12 monthly liver ultrasound, recommended with long term use.</li> </ul> |
| Anti-fibrinolytics: tranexamic acid                             | <ul style="list-style-type: none"> <li>Only recommended for prophylaxis by some.</li> <li>Oral or IV administration.</li> </ul>  |

<sup>15</sup> Johnson NM, Phillips MA. New Treatments for Hereditary Angioedema. STL Vol 23 (1); Jan 2018. Accessed May 2018 at <http://www.skintherapyletter.com/angioedema/new-treatments/>

<sup>16</sup> Maurer M, Magerl N. Hereditary angioedema: an update on available therapeutic options. *JDDG*; 2010 8:663-672. DOI: 10.1111/j.1610-0387.2010.07450.x. Accessed May 2018 at

[https://www.academia.edu/18902739/Hereditary\\_angioedema\\_an\\_update\\_on\\_available\\_therapeutic\\_options](https://www.academia.edu/18902739/Hereditary_angioedema_an_update_on_available_therapeutic_options)

<sup>17</sup> FDA approved label for Haegarda. Accessed May 2018 at

<https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM564335.pdf>

| Treatment option | Characteristics   |
|------------------|---|
|                  | <ul style="list-style-type: none"> <li>Common adverse reactions include: minor GI upsets, headache, myalgia.</li> <li>Efficacy not established but may have a place for prophylaxis in prepubertal children.</li> </ul> |

In addition to advice regarding new treatment options, more recent guidelines have increasingly advocated immediate initiation of treatment of acute attacks with home-based care, so as to minimise the delay to treatment and the effect of attacks on quality of life. The guidelines recommend that every patient with HAE should be considered for self/caregiver administration and home therapy; should be provided with the training required to enable this; should have sufficient on-demand treatment on hand for two attacks; and should carry on-demand treatment at all times.

#### *Management of HAE with normal C1-INH levels and function (HAE type III)*

In general, the guidelines recognise that the underlying pathophysiology of this condition differs from HAE with deficient or dysfunctional C1-INH and specifically exclude this condition from the management recommendations contained in the guidelines. The HAE position paper produced by the ASCIA;<sup>18</sup> notes that it is a very rare condition and that '*This subtype will not be discussed in this document*'. The 2017 International WAO/European Academy of Allergy and Clinical Immunology (EAACI) updated guideline for the management of HAE was limited to HAE with deficient C1-inhibitor (type I) and HAE with dysfunctional C1-inhibitor (type II) and states that '*although HAE nC1-INH (HAE with normal C1-INH) shares some clinical features and, possibly, therapeutic options with HAE-I/II, this guideline is for HAE-I/II*'.

#### **Treatment options in Australia**

Treatment options available to the Australian clinician and patient will depend on the regulatory and funding status of newer agents.

The TGA has approved two human plasma derived forms of C1-INH concentrate, Cinryze and Berinert for treatment of acute attacks, with Cinryze also approved for short and long term prophylaxis. The preparation for SC administration, Haegarda, has been approved by the FDA for prophylaxis but has not been approved by the TGA to date. Oral tranexamic acid and danazol have been approved by the TGA for use in HAE. The regulatory status of the newer acute attack treatments is as follows: recombinant C1-INH, conestat-alfa, has been approved by the FDA and the European Medicines Agency (EMA), but not the TGA to date; icatibant has been approved by the TGA, EMA and FDA; ecallantide is approved by the FDA and received Orphan designation from the TGA in 2011.

Icatibant, danazol and tranexamic acid are included on the Pharmaceutical Benefits Scheme. Berinert (but not Cinryze) is funded by the National Blood Authority (NBA) for the following indications for type I or II HAE<sup>19</sup>:

- treatment of acute attacks
- pre-procedural (short term) prophylaxis for high risk procedures such as dental work, head or neck surgery, or surgery requiring intubation
- second line as routine (long term) prophylaxis for patients who experience the equivalent of eight or more acute attacks per month.

<sup>18</sup> Australasian Society of Clinical Immunology and Allergy (ASCIA) Health Professionals Position Paper on Hereditary Angioedema (2017).

<sup>19</sup> National Blood Authority, Plasma and recombinant product procurement. See <https://www.blood.gov.au/plasma-and-recombinant-product-procurement>

The ASCIA position paper takes into account funding and access in Australia.<sup>18</sup> According to this paper, either icatibant or Berinert may be used for acute attacks (although icatibant may be preferred due to SC administration and presentation as a ready-to-use syringe); short-term prophylaxis is by danazol with use of Berinert limited to high risk procedures; long term prophylaxis is by danazol with Berinert used second line in accordance the NBA approved indication. As noted above, this position paper also specifically excludes patients with HAE with normal C1-INH.

### **Lanadelumab**

As described above, lanadelumab is a mAb that targets active pKal. The proposed mechanism for lanadelumab is that inhibition of pKal will result in reduced release of bradykinin and that this, in turn, will reduce HAE attacks.

Possible off-target effects of lanadelumab could include those related to dysfunction of the broader kinin-kallikrein system and those related to inhibition of other serine proteases. The sponsor notes that congenital prekallikrein deficiency, which is associated with a nearly complete absence of pKal activity, is not associated with any apparent consequences.

### **Clinical rationale**

According to the sponsor, the purpose of the application is *'to seek approval for the use of lanadelumab (also known as DX-2930 and SHP643) for routine prophylaxis to prevent attacks and control the symptoms of hereditary angioedema (HAE) in patients 12 years and older'*.

The submission describes the pharmacological class, purported mechanism of action (inhibition of pKal reducing the release of bradykinin and, in turn, reducing vascular leak and oedema) and the pharmacokinetic properties that support administration every 2 to 4 weeks. It also states that the dose of 300 mg fortnightly had maximal efficacy although lanadelumab at doses of 300 mg every 4 weeks and 150 mg every 4 weeks were also demonstrated to be efficacious.

The relevance of pKal as a target for the treatment of HAE was discussed in the submission, with the efficacy of the FDA-approved pKal inhibitor, ecallantide, referred to in support. The action of lanadelumab as an inhibitor of pKal was described. The need for improved prophylactic treatments was discussed in terms of the serious morbidity and mortality associated with HAE. Current treatments for both acute attacks and prophylaxis were briefly listed. Recommendations in current guidelines for the use of C1-INH concentrates or attenuated androgens were largely discounted with the statement that these agents have *'numerous contraindications, therapeutic class adverse events (AEs), risk factors for AEs, tolerance to therapy, and overall suboptimal control of HAE due to the need higher or more frequent dosing, threat of breakthrough attacks, and low attack-free rates'*. It was argued that these deficiencies in current treatments represented an unmet need with this illustrated by a 2015 survey of US HAE patients reported as finding that *'47 (94%) were using C1-INH for HAE prophylaxis, reported clinical issues pertaining to IV access and complications thereof and breakthrough attacks with a mean of 2.3 attacks per month, during the previous 6 months'*. The statement was made that *'this substantial unmet need exists in adolescents as well as adults, as the pattern of attacks is similar in these two populations'*.

### **Evaluator's commentary on the background information**

The clinical rationale for the development of lanadelumab is reasonable and the proposed mechanism of action is plausible. The evaluator accepts that lanadelumab would offer some advantages over current long term prophylaxis treatment options with the

avoidance of intravenous administration twice weekly of C1-INH and the avoidance of androgen side effects.

The evaluator is not convinced that there is an unmet need for all patients with HAE, given that there are currently accepted and effective long term prophylaxis treatment options. The sponsor has described these options as inadequate for a number of reasons (see quoted statement above). Danazol, the most likely first line agent in Australia is described in the ASCIA position paper as effective and well tolerated despite the many potential side effects, with a recent survey quoted as showing that *'79% of patients experienced adverse effects from danazol, but only 25% discontinued treatment because of these; the benefits were great with > 90% reduction in episode frequency in > 70% of patients, and a 95% reduction in the frequency of laryngeal episodes'*. The evaluator does agree that an unmet need exists for adolescents, given the potential for growth retardation with androgens and the potential difficulties in obtaining intravenous access.

The evaluator considers that the background information and clinical rationale as provided in the Clinical Overview is deficient in the following respects:

- *HAE type in the target population*: the discussion presented is limited to HAE with deficient or dysfunctional C1-INH (types I and II). No discussion of HAE with normal C1-INH (type III) is provided. This issue and the proposed wording of the indication is discussed further below.
- *Age groups in the target population*: the indication proposes that lanadelumab be used in patients with HAE aged 12 years or more. The rationale provided does not present the argument for use in adolescents beyond the statement quoted above, that *'the pattern of attacks is similar in these two populations'*. A more comprehensive discussion was expected given that there were no dedicated paediatric studies. The evaluator notes that the protocol for the main efficacy study, Study DX-2930-03, provides the following information regarding children with HAE:
  - *'Like adults, children with HAE can suffer from recurrent and debilitating attacks. Symptoms may present very early in childhood, and upper airway angioedema has been reported in HAE patients as young as the age of 3.<sup>20</sup> In one case series of 49 paediatric HAE patients, 23 had suffered at least one episode of airway angioedema by the age of 18.<sup>21</sup> An important unmet medical need exists among children with HAE, especially adolescents, since the disease commonly worsens after puberty.<sup>22,23</sup>*
- *Role in acute attacks*: The discussion presented in the Clinical Overview was based around the potential role of lanadelumab in long term prophylaxis. A role in acute treatment or short term prophylaxis is not proposed or discussed. The sponsor initially proposed that the indication be *'for routine prophylaxis to prevent attacks and control the symptoms'* of HAE. This wording does not clearly limit use to long term prophylaxis. In response to a question from the evaluator, the sponsor has agreed to the removal of the phrase *'the control of symptoms'*.

<sup>20</sup> Bork K, et al. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency *Arch Intern Med*. 2003; 163: 1229-12235

<sup>21</sup> Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency *Allergy Asthma Clin Immunol*. 2010; 6(1):18. doi: 10.1186/1710-1492-6-18

<sup>22</sup> Bennett G and Craig T. Hereditary angioedema with a focus on the child. *Allergy Asthma Proc*. 2015; 36: 70-73.

<sup>23</sup> Zuraw BL. Hereditary angioedema: a current state-of-the-art review, IV: short- and long-term treatment of hereditary angioedema: out with the old and in with the new? *Ann Allergy Asthma Immunol*. 2008;100(1 Suppl 2):S13-8

## Guidance

The following guidelines were referred to in the performance of this evaluation:

- EMA Guideline on development, production, characterisation and specification for monoclonal antibodies and related products. EMA/CHMP/BWP/532517/2008.
- ICH Harmonised Guideline Addendum to ICH E11: clinical investigation of medicinal products in the paediatric population.
- ICH Topic E 1 Population Exposure: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. Note for guidance on population exposure: The extent of population exposure to assess clinical safety (CPMP/ICH/375/95).
- Clinical investigation of medicinal products for long-term use.
- ICH E14 Technical requirements for registration of pharmaceuticals for human use.
- ICH Topic Q6B. Notes for guidance on specifications: test procedures and acceptance criteria for biotechnological/biological products (CPMP/ICH/365/96).
- ICH Topic Q5E Comparability of biotechnological/biological products. note for guidance on biotechnological/biological products subject to changes in their manufacturing process (CPMP/ICH/5721/03).

## Contents of the clinical dossier

The submission includes the following clinical study reports:

- Reports of biopharmaceutic studies with listing of:
  - 26 bioanalytical and analytical methods for human studies
- Clinical study reports for
  - Study DX-2930-01: healthy subject pharmacokinetic and initial tolerability study
  - Study DX-2930-02: HAE patient pharmacokinetic and initial tolerability study
  - Study DX-2930-03: main efficacy study for the proposed indication
  - Study DX-2930-04: open label extension study for Study DX-2930-03.
- Population pharmacokinetic reports with these listed as:
  - Population pharmacokinetic, pharmacokinetic/pharmacodynamic and exposure-response analysis of SHP643 (DX-2930) for long term prophylaxis against acute attacks of hereditary angioedema (Part 1 and Part 2)
  - A separate analysis plan was provided for each population pharmacokinetic report.
- Other reports included:
  - Potential for cardiovascular effects of plasma kallikrein inhibitors: a review of the literature and of data from DX-2930-03
  - Lanadelumab QT evaluation plan assessment
  - ECG assessment report for Study DX-2930-03 and Study DX-2930-04
  - Review of lanadelumab (DX-2930) hepatic events in Phase III studies
  - Paediatric data for lanadelumab (SHP643, DX-2930)
  - Evidence supporting the Angioedema Quality of Life (AE-QoL) questionnaire in patients with HAE.

- References with 106 publications listed.

### **Paediatric data**

The proposed indication includes patients with HAE aged 12 years or more. Patients aged < 12 years were excluded from the clinical studies. Patients aged 12 to < 18 years were included in Studies DX-2930-03 and DX-2930-04.

### **Good clinical practice**

The sponsor's Clinical Overview states that all clinical studies with lanadelumab were conducted in accordance with the ICH GCP guidelines, the principles described in the Declaration of Helsinki, the US Code of Federal Regulations, and the European Union (EU) Clinical Trials Directive, as well as any other applicable local/regional regulations and guidelines regarding the conduct of clinical studies.

### ***Evaluator's commentary on the clinical dossier***

The dossier describes a clinical development programme for lanadelumab with one Phase Ia study, one Phase Ib study, one randomised double-blind placebo-controlled Phase III study and one open label extension study. Each of these studies included a small number of participants and a range of lanadelumab doses and dosing intervals.

There were no dedicated PK studies of special populations and no investigations of bioavailability, distribution, metabolism and excretion. There was limited investigation of primary pharmacodynamic effects and very limited investigation of secondary PD effects. The presentation of efficacy was limited to the single Phase III 'pivotal' study, with the open label extension study considered supportive by the sponsor. The Phase Ib study was described as providing proof-of-concept. The presentation of safety included data from all studies and was supplemented by reviews of hepatic events and cardiovascular events in the Phase III study.

Issues identified with the dossier include:

- As noted above, the proposed indication initially included the phrase '*control of symptoms*', although the rationale and evidence provided in the dossier is limited to long-term prophylaxis. The sponsor has agreed to remove this phrase.
- The clinical studies included in the dossier specifically excluded HAE with normal C1-INH (type III). The background information provided also did not refer to these patients. However, the proposed wording of the indication does not limit the treatment population to patients with HAE with deficient or dysfunctional C1-INH (types I or II) and is, therefore, not consistent with the background presented in the Clinical Overview or the HAE population investigated in the clinical trial. This issue has been raised with the sponsor and is discussed further below.
- The proposed indication is for a target population aged 12 years or older. The dossier does not include any dedicated studies performed in adolescents. Clinical experience in this population is limited to 10 patients aged 12 to 17 years in the main efficacy study and an additional 13 patients in the open label extension study. Whether this is an adequate basis for approval of the use of lanadelumab in this population has been raised with the sponsor and is discussed further below. Also of note is that the reported experience in patients aged more than 65 years is even more limited.
- Neither the optimal dose nor the optimal dosing frequency has been determined in the studies presented. The PI proposes that 'maximal efficacy was observed at doses of 300 mg every 2 weeks and is the recommended dose. Doses of 300 mg every 4 weeks and 150 mg every 4 weeks have also been studied'. This recommendation for the proposed dose of 300 mg every 2 weeks is largely based on 'numerically higher

responses' for this regimen in the main efficacy study. This issue has been raised with the sponsor.

## Pharmacokinetics

**Table 7: Studies providing pharmacokinetic data**

| Pharmacokinetics topic                  | Subtopic                               | Study ID                               |
|---|--|--|
| Pharmacokinetics in healthy adults      | General pharmacokinetics - Single dose | DX-2930-01                             |
|   | - Multi-dose                           | N/I                                    |
|   | Bioequivalence - Single dose           | N/I                                    |
|   | - Multi-dose                           | N/I                                    |
|   | Food effect                            | N/A                                    |
| Pharmacokinetics in special populations | Target population §- Single dose       | N/I                                    |
|   | - Multi-dose                           | DX-2930-02<br>DX-2930-03<br>DX-2930-04 |
|   | Hepatic impairment                     | N/I                                    |
|   | Renal impairment                       | N/I                                    |
|   | Neonates/infants/children/adolescents  | N/I                                    |
|   | Elderly                                | N/I                                    |
|   | Other special population               | N/I                                    |
| Genetic/gender related pharmacokinetics | Males versus females                   | N/I                                    |
|   | Other genetic variable                 | N/I                                    |
| Pharmacokinetics interactions           | Any drug                               | N/I                                    |
| Population pharmacokinetics analyses    | Healthy subjects                       |  |
|   | Target population                      |  |
|   | Part 1                                 |  |
|   | Part 2                                 |  |
|   | Other                                  |  |

§ Subjects who would be eligible to receive the drug if approved for the proposed indication; N/A Not applicable; N/I Not investigated by dedicated study/studies.

### Evaluator's conclusions on pharmacokinetics

The sponsor has provided a limited investigation of the pharmacokinetics of lanadelumab.

In vitro investigations found that lanadelumab is a highly specific pK<sub>1</sub> inhibitor that did not inhibit any of the 20 serine proteases that were tested at a concentration (at least 1 µM) exceeding the maximum concentration expected in patient plasma.

Clinical pharmacokinetic investigations were limited to measurements of plasma concentration of lanadelumab after single or repeated dosing. No investigations of

distribution, metabolism or excretion have been performed. This is consistent with the approach taken with other therapeutic mAbs where these characteristics are assumed to follow those of endogenous antibodies, that is, distribution limited to vascular and interstitial spaces and elimination by proteolytic catabolism to smaller peptides and amino acids.

Measurement of plasma lanadelumab was by two different assays, both of which are reported to measure free lanadelumab. Cross-validation of the assays was not performed. One assay was used in the study of healthy subjects, in which rich sampling was performed. A different assay was used in the three clinical studies of HAE patients. Rich sampling was performed in one of these studies (Study DX-2930-02), with sparse sampling in the two Phase III studies.

The pharmacokinetics of lanadelumab in healthy subjects was found to differ from that of patients with HAE, with lower clearance and longer half-life. The sponsor speculated that this may be due to different levels of plasma kallikrein but acknowledged that it may also be due to differences in the assays used.

The pharmacokinetic profile, as demonstrated in patients with HAE in Study DX-2930-02, was characterised by:

- slow absorption that was independent of dose. The average time to peak plasma concentration was between 3 and 8 days;
- exposure, as shown by measures of AUC, was dose-dependent;
- clearance was linear and independent of dose;
- prolonged half-life that was independent of dose; and
- low distribution that was independent of dose.

These characteristics are consistent with those of therapeutic mAbs and endogenous IgG.

The pharmacokinetic parameters in the patients in Study DX-2930-02 who received two doses of 300 mg lanadelumab two weeks apart (n = 5) were:

- Mean  $C_{max}$  (ng/mL): 27,460 (SD 14,452)
- Mean  $T_{max}$ : 18.2 days (SD 1.45).
- Mean AUC (day.ng/mL): 451,800 (SD 226,801)
- CL/F (L/day): 1.00 (SD 0.9)
- Vd/F (L): 17.4 (10.6)
- $T_{1/2}$  (days): 14 (SD 3.25)

$T_{max}$  and  $C_{max}$  occurred approximately 4 days after the second dose.

There were no dedicated studies to investigate the effects of race, renal impairment, hepatic impairment or special populations (including adolescents or the elderly) on lanadelumab pharmacokinetic. There were no dedicated investigations of drug-drug interactions.

The evaluator accepts that such a limited pharmacokinetic investigation is not unusual in the development of monoclonal antibodies and that it is not unreasonable that lanadelumab be assumed to behave in a similar fashion to other monoclonal antibodies. The evaluator also acknowledges that, in situations where there is a very rare condition, there are practical limitations to the extent of the investigations that can be performed. However, it is important that the limits of the available information are explicit in the PI so that prescribing clinicians are aware of the uncertainties.



Proposed statements in the PI regarding pharmacokinetic in special groups and drug-drug interactions are based on the results of the population pharmacokinetic analyses and additional post hoc analyses. The evaluator has concerns regarding the validity of the pharmacokinetic model and its predictive ability as development of the model has assumed that the plasma lanadelumab concentrations measured by the two different assays are interchangeable and given that it has predicted lower exposure with every 2 weeks dosing regimen compared to every 4 weeks regimen. The population pharmacokinetic analyses regarding special populations were also limited by the small numbers of participants in many of the sub-groups. On this basis, the evaluator recommends that any statements based on population pharmacokinetic analyses in the PI should be cautious with the population pharmacokinetic analyses clearly identified as the basis of these statements and that the limits of such statements should be explicit.

The evaluator is of the opinion that weight-based dosing should be considered. Both population pharmacokinetic analyses found that lower body weight was associated with higher lanadelumab exposure. This finding is consistent with the pharmacokinetic reported for other mAbs. Population pharmacokinetic/pharmacodynamic analyses have also demonstrated that the mean concentrations and exposures achieved with all three regimens investigated in Study DX-2930-03 are, in general, considerably in excess of the 50% inhibitory concentration ( $IC_{50}$ ) needed to achieve the pharmacodynamic end-points of pKal inhibition (as shown by cleaved HMWK level) and reduction in monthly attack rate. Assuming that these are real findings, and given that the main efficacy study could not demonstrate any significant difference in efficacy between the regimens,<sup>24</sup> then there would appear to be no need to administer the same dose to patients with lower body weight. The sponsor proposes that lanadelumab be provided in two vial strengths (150 mg in 1 mL and 300 mg in 2 mL) and that the recommended dose in all patients should be 300 mg every 2 weeks. The evaluator recommends that the dose of 150 mg should be considered the preferred dose in patients of lower body weight, including adolescents, and that this information should be included in the PI.

## Pharmacodynamics

### Studies providing pharmacodynamic data

**Table 8: Studies providing pharmacodynamic data**

| Pharmacodynamic Topic | Subtopic                   | Study ID                                |
|-----------------------|----------------------------|---|
| Primary Pharmacology  | Effect on pKal activity    | DX-2930-01<br>DX-2930-02<br>DX-2930-03  |
|                       | Effect on cleavage of HMWK | DX-20903-01<br>DX-2930-02<br>DX-2930-03 |
|                       | Frequency of HAE attack    | DX-2930-02<br>DX-2930-03                |

<sup>24</sup> Clarification: the study was not designed or powered to demonstrate differences between treatment groups

| Pharmacodynamic Topic  | Subtopic  | Study ID  |
|--|---|---|
|  | Use of rescue C1-INH                                | DX-2930-03  |
| Secondary Pharmacology   | Effect on anti-drug antibodies                      | DX-2930-02<br>DX-2930-03<br>DX-2930-04  |
|  | Effect on ECG                                       | No dedicated studies  |
| Gender, other genetic, and age related differences in pharmacodynamic response | Effect of gender, any genetic characteristic or age | No dedicated studies  |
| Pharmacodynamic interactions   | Any drug  | No dedicated studies  |
| Population pharmacodynamic and pharmacokinetics-pharmacodynamic analyses       | Healthy subjects                                    |   |
|  | Target population                                   | pharmacokinetics/pharmacodynamic analyses<br>Exploratory exposure-response analyses (efficacy)<br>Exploratory exposure-response analyses (safety) |

### Evaluator's conclusions on pharmacodynamics

Pharmacodynamic data has been included from each of the three clinical trials investigating the use of lanadelumab in the prevention of HAE attacks in patients with HAE types I and II and from the first-in-human study in healthy subjects. The exploratory biomarkers, activity of pKal and cleaved HMWK level, were used to investigate pharmacodynamic effects. The use of these biomarkers is appropriate to the proposed mechanism of action whereby lanadelumab inhibits the activity of pKal and reduces the production of bradykinin and cleaved HMWK.

Overall, the pharmacodynamic results showed that treatment with lanadelumab resulted in the expected biological effects, with a decrease in pKal activity and decrease in cleaved HMWK production in both healthy subjects and patients with HAE types I and II. Pharmacodynamic results were consistent across the clinical studies. The effects on pKal activity and cleaved HMWK level appear to be concentration and dose dependent at lower levels but exhibit a ceiling effect at the higher doses/concentrations investigated in the Phase III studies. Doses up to 30 mg had no demonstrable effect on pKal activity whereas doses of 300 mg and 400 mg seemed to result in a similar inhibition. For cleaved HMWK levels, a reduction was not apparent for the dose of 100 mg and a similar reduction was seen with both the 300 mg and the 400 mg dose. The pKal inhibition appeared to be prolonged, with cleaved HMWK levels returning to Baseline after 120 days. The maximum reduction in cleaved HMWK resulted in cleaved HMWK levels higher than those observed in healthy subjects who had not received lanadelumab. The reduction in cleaved HMWK achieved with 300 mg and 400 mg doses was similar to that achieved with a therapeutic concentration of the pKal inhibitor ecallantide. The time course for the changes in pKal activity and cleaved HMWK levels followed the time course for lanadelumab plasma concentrations.

Exploratory analyses were performed to link the biological effects to clinical effects. These found a reduction in the average monthly rate of reported HAE attacks in HAE patients receiving lanadelumab. The time course for this followed the time course for lanadelumab plasma concentration increase and the cleaved HMWK level decrease for the lanadelumab treatment groups. A similar reduction in HAE attack rates was reported for each of the treatment regimens investigated in the Phase III study. The evident, but smaller, decrease in HAE attack rate in placebo treated patients was unexplained but may reflect the inherent variability in the pattern of HAE attacks in individuals. The prolonged effect in terms of reduction in HAE attack frequency during the dose-and-wait period in the rollover patients of Study DX-2930-04 raises the possibility that 'drug holidays' (for example, after 6 months continuous treatment) could be considered.

The investigation of the effect of lanadelumab on C1-INH levels found no effect; this is consistent with the proposed mechanism of action.

There was little investigation of secondary pharmacodynamic effects.

Plasma kallikrein is a member of a large and important family of serine proteases that all share the same catalytic mechanism and key active amino acids. *In vitro* testing found that lanadelumab was found to be specific to pKal and did not inhibit any of 20 other serine proteases. Of note is that there was no demonstrated inhibition of tissue kallikrein so it is expected that lanadelumab would not alter the production of bradykinin through this route. However, these investigations were performed *in vitro* and have not been confirmed *in vivo*.

The potential for lanadelumab to have other secondary effects through actions on the kinin-kallikrein pathway cannot be excluded on the information currently available. However, the following observations indicate that clinically important effects are unlikely. The reduction in cleaved HMWK observed with lanadelumab in HAE patients remained elevated in comparison to healthy subjects, suggesting that there was still capacity for normal responses to tissue injury to occur. The alternative pathway for the production of bradykinin (tissue kallikrein and lys-bradykinin) should not be affected given the specificity of lanadelumab to plasma kallikrein. Congenital prekallikrein deficiency is not usually associated with any health problems. Prolonged aPTT was observed in rats treated with lanadelumab but was not associated with a bleeding tendency. There was a similar effect in humans, although the aPTT remained within normal range. This was not associated with major bleeding effects.

Serial ECG monitoring in the clinical studies found no apparent effect of lanadelumab on ECG parameters.

There have been no investigations for pharmacodynamic drug interactions, except for an exploratory analysis of the effect of concomitant administration of rescue medications (C1-INH, icatibant and ecallantide) in a pharmacokinetic/pharmacodynamic analysis. This is inadequate to exclude interactions. Theoretically, the efficacy of C1-INH concentrate and icatibant in the treatment of acute HAE attacks should not be affected by concomitant treatment with lanadelumab. C1-INH concentrate should act to further inhibit pKal and icatibant should still bind to the bradykinin B2 receptor. However, according to the FDA approved label, ecallantide is a potent, selective, reversible inhibitor of pKal. It appears to act similarly to lanadelumab as it binds to and blocks the active binding site of kallikrein. Lanadelumab may compete with ecallantide for the kallikrein binding site and alter its efficacy in the treatment of acute attacks.

The development of an anti-lanadelumab antibody assay proved problematic and limited the investigation of immunogenicity. The development of anti-drug antibodies in patients with HAE who were treated with lanadelumab appeared to occur infrequently.

Overall, the pharmacodynamic investigations were limited but support the purported mechanism of action. The biological actions of pKal inhibition with reduced cleaved HMWK production were demonstrated. It is plausible that these actions will result in reduced bradykinin production and reduced HAE attacks. Pharmacokinetic/pharmacodynamic analyses demonstrated a greater reduction in the average monthly HAE attacks in lanadelumab treated patients compared to placebo treated patients. The process of pKal inhibition by lanadelumab appears to be saturated at the concentrations seen with the dosing regimens proposed for approval, with no significant difference in the reduction in cleaved HMWK level or average monthly HAE attack rate evident across the three treatment regimens investigated in the Phase III study.

The limited investigation of secondary pharmacodynamic effects found no effects of lanadelumab on ECG parameters; mild prolongation of aPTT without associated bleeding; and low immunogenicity.

No pharmacodynamic drug interaction studies were conducted. Of theoretical concern is possible competition between lanadelumab and ecallantide for the active binding site on pKal, with this potentially decreasing the effectiveness of ecallantide in the treatment of acute attacks. Of note is that this may not be of importance in the Australian setting as ecallantide is not approved by the TGA.

## **Dosage selection for the pivotal studies**

According to the protocol for the main efficacy study, Study DX-2930-03, the dose selection in the study was based on the pharmacodynamic bioactivity, pharmacokinetic, safety, and efficacy of DX-2930 from the Phase I clinical studies and nonclinical studies. The study investigated three different dosing regimens: 150 mg every 4 weeks, 300 mg every 4 weeks and 300 mg every 2 weeks.

## **Non-clinical Studies**

Pharmacokinetic profiles of lanadelumab were evaluated following single and repeat dose SC administration in rats (4 weeks) and cynomolgus monkeys (4 weeks and 6 months). In both rats and cynomolgus monkeys, lanadelumab was reported to exhibit typical pharmacokinetic behaviour as expected from an IgG1 molecule with low clearance, low volume of distribution, and long half-lives. Single dose SC toxicity studies at doses up to and including 50 mg/kg found no overt toxicity. Repeat dose toxicity studies of 5, 25, or 50 mg/kg also reported no adverse findings. In repeat dose studies in rats a higher mean aPTT was noted in lanadelumab treated groups but was not associated with abnormal bleeding patterns. Effects on aPTT were not observed in repeat dose studies in cynomolgus monkeys. Lanadelumab was highly immunogenic in rats but not in cynomolgus monkeys.

## **Dose finding studies**

There were two clinical studies that contributed to dose selection for the main efficacy and safety study:

- Study DX-2930-01: a Phase Ia first in human study in healthy subjects
- Study DX-2930-02; - a Phase Ib study in patients with HAE

Study DX-2930-01 was a Phase Ia first-in-human study that randomised healthy subjects to placebo or to receive a single dose of lanadelumab of 0.1 or 0.3 or 1.0 or 3.0 mg/kg. The maximum dose received by an individual was 303 mg. Pharmacodynamic effects of inhibition of plasma kallikrein activity and reductions in cleaved HMWK level (expressed as % 2-chain HMWK) compared to placebo were observed in subjects treated with

3.0 mg/kg of lanadelumab but not in those treated with 0.1 or 0.3 mg/kg of lanadelumab. The reduction in cleaved HMWK, where observed, persisted to Day 28. The pharmacokinetic was considered to be consistent with SC administration of a mAb. The study identified no dose limiting toxicities, serious adverse events, or any other safety concerns.

Study DX-2930-02 was a Phase Ib study that investigated two doses of lanadelumab or placebo administered 2 weeks apart in patients with HAE type I or II. Study participants who were randomised to lanadelumab treatment, were further randomised to one of four lanadelumab dose groups: 30, 100, 300, and 400 mg. Inhibition of pKal was evident in plasma samples collected from the 100, 300, and 400 mg dose groups but not in the 30 mg dose group. Significant reduction from Baseline in mean levels of cleaved HMWK, were observed in the 300 mg and 400 mg dose groups but not in the 30 mg or 100 mg dose group or the placebo group.

The pre-specified efficacy analysis was limited to subjects in the 300 mg, 400 mg, and placebo dose groups with a historical baseline attack rate of at least 2 attacks over the last 3 months prior to enrolment. This found no substantial change in the HAE attack rate between baseline and treatment in the placebo group but substantial and significant reductions in the HAE rate between Baseline and treatment for both of the treatment groups compared to placebo. The study identified no dose-limiting toxicities, serious adverse events, or any other safety concerns.

On the basis of the above considerations, three separate dosing regimens were selected for evaluation in the Phase III study: 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks. The study protocol for this study notes that the three proposed dose-regimen combinations would be expected to provide a 6 fold range of steady-state trough concentrations with doses of 150 mg or 300 mg administered every 4 weeks expected to result in steady-state trough concentrations of approximately 4,750 and 9,500 ng/mL respectively and steady-state trough concentrations following 300 mg every 2 weeks of approximately 27,000 ng/mL.

There were three separate dose-regimens investigated in the main efficacy study, Study DX-2930-03: 300 mg SC every 2 weeks; 300 mg SC every 4 weeks; and 150 mg SC every 4 weeks. The selection of these dosing regimens is reasonable on the basis of the information obtained through the Phase I studies. It is important to note that the efficacy results of the Phase III main efficacy study was not able to establish the optimal dosing regimen. As noted in the Clinical Overview, 'the study was not designed to compare the treatment effect within the three randomized lanadelumab treatment arms'.

## **Efficacy**

### **Studies providing efficacy data**

The sponsor has presented Study DX-2930-03 as pivotal for efficacy, with the open label extension Study DX-2930-04 described as supportive. The Phase Ib Study DX-2930-02, was presented as providing 'proof-of-concept'. The only other study in the clinical development programme, Study DX-2930-01, investigated a single dose of lanadelumab in healthy participants.

### **Evaluator's conclusions on efficacy**

The sponsor has presented Study DX-2930-03 as pivotal for efficacy, with the open label extension Study DX-2930-04 described as supportive. The Phase Ib Study DX-2930-02, was presented as providing 'proof-of-concept'. Efficacy analyses in the studies were all

based on some measure of acute HAE attacks. This is appropriate and consistent with studies investigating other long term prophylactic treatments for HAE.

The main efficacy study, Study DX-2930-03, was a Phase III, multicentre, randomised, double blind, placebo controlled, parallel group trial that investigated three different lanadelumab treatment regimens (150 mg every 4 weeks, 300 mg every 4 weeks and 300 mg every 2 weeks) administered over a 26 week treatment period. The study enrolled patients with confirmed HAE type I or II who were aged 12 years or more and who had a demonstrated baseline HAE attack frequency of 1 per month. Patients who were already receiving long term prophylaxis could enrol but only after cessation of this therapy and a washout period. The primary efficacy endpoint was the rate of investigator confirmed HAE attacks during the treatment period. Secondary endpoints were of other measures of HAE attacks.

There were 125 participants in the study, randomised as follows: placebo n = 41; 150 mg every 4 weeks n = 28; 300 mg every 4 weeks n = 29; 300 mg every 2 weeks n = 27. The study met its primary endpoint with a reduction in investigator confirmed HAE attack rates during the treatment period compared to placebo of more than 70% for each of the lanadelumab treatment arms ( $p < 0.001$ ). Analyses of HAE attacks requiring acute treatment, laryngeal attacks and high morbidity attacks found that these more severe attacks were similarly reduced, indicating that the reduction is not limited to minor HAE attacks. Also of importance is that a higher percentage of subjects (31.0% to 44.4%), in the three lanadelumab treatment arms were 'attack free' compared to placebo (2.4%) throughout the 26 week treatment period. Robustness of the results was demonstrated as the results for secondary efficacy end-points, sensitivity and most sub-group analyses were all consistent with the result for the primary end-point. No distinction can be made regarding efficacy for the three lanadelumab treatment regimens. There were some minor numerical differences in results across the treatment arms but these were not consistent and the study was not designed or powered to compare the treatment effect within the three lanadelumab treatment arms. Efficacy was not established in the following sub-groups:<sup>25</sup> race other than white, weight  $\geq 100$  kg, weight  $< 50$  kg, baseline rate 1 to  $< 2$ , HAE type II, age  $< 18$  years, age  $> 65$  years. Efficacy is unclear in patients with presumed milder disease, given the discordant results for patients with a baseline HAE attack rate of 1 to  $< 2$  and patients not on prior long term prophylaxis.

The open label extension study (OLE), Study DX-2930-04, was included as supportive of efficacy. This study enrolled patients from all treatment arms of Study DX-2930-03, with 109 of 125 participants electing to continue into the OLE (rollover patients). Participants who were not part of Study DX-2930-03 could also participate (non-rollover patients). A lower rate of baseline HAE attacks was accepted for these patients. Treatment regimens differed between the rollover and non-rollover patients: rollover patients received a single dose of lanadelumab and then commenced a dose-and-wait phase with lanadelumab 300 mg every 2 weeks commenced with the first HAE attack; non-rollover patients commenced lanadelumab 300 mg every 2 weeks from study entry.

The study enrolled 109 rollover patients and 103 non-rollover patients, including 19 patients from Study DX-2930-02. Interpretation of the efficacy results of this study is limited by the absence of a placebo arm, open label administration, inclusion of groups with differing baseline attack rates and different treatment approaches. Given these factors, this study can provide limited support. However, the range of median attack rates during the treatment periods of lanadelumab 300 mg every 2 weeks was between 0.0 and 15.4 attacks per month and consistent with the rates reported in the main efficacy study. Rollover patients from active treatment arms in Study DX-2930-03 achieved similar

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<sup>25</sup> Clarification: efficacy was not established because the efficacy data was limited as the number of subjects in these subgroups were small

control according to mean HAE attack rates as were achieved in the earlier study, suggesting that the break in treatment during the dose-and-wait phase did not affect efficacy on treatment resumption.

There were 70 patients with 1 year of cumulative experience (inclusive of the dose-and-wait period) across Studies DX-2930-03 and DX-2930-04. Median HAE attack rates achieved with lanadelumab treatment in Study DX-2930-03 were maintained during Study DX-2930-04, suggesting that tolerance over this period of time does not develop. However, there were 3 participants in Study DX-2930-03 who were categorised as responders in this study and who were categorised as non-responders in Study DX-2930-04. This was attributed to the occurrence of life-changing stressful events triggering HAE attacks, rather than the development of tolerance.

The Phase Ib Study DX-2930-02 provided proof of concept. The analysis of those HAE participants who received two doses of 300 mg or 400 mg of lanadelumab and who had a baseline attack rate of at least 2 attacks in the 3 months found a 100% reduction in HAE attacks versus placebo for 300 mg lanadelumab ( $p < 0.0001$ ) and an 88% reduction versus placebo for 400 mg lanadelumab ( $p = 0.005$ ). The numbers analysed were small: lanadelumab 300 mg  $n = 4$ ; lanadelumab 400 mg  $n = 11$ ; placebo  $n = 11$ .

The results from the clinical studies are all consistent and indicate a significant and clinically important reduction in the incidence of acute HAE attacks in patients with moderate to severe HAE type I who receive prophylactic treatment with lanadelumab. Any conclusions must, however, be tentative given the small overall number of patients investigated, the inherent intra-individual variability in HAE attack rate and pattern and possible confounding effects of factors outside the control of the study, such as personally stressful events. Efficacy is not established in sub-groups of small numbers.

### ***Optimal dose for efficacy***

The evaluator does not consider that the optimal dosing regimen for lanadelumab has been determined. As acknowledged by the sponsor, the pivotal study was not designed to compare the treatment effect within the three randomised lanadelumab treatment arms. The evaluator is of the opinion that the small numerical differences in the treatment arms in Study DX-2930-03 reflect small numbers and the inherent intra-individual variability in the pattern of HAE attacks rather than greater efficacy with one treatment arm. This issue has been raised with the sponsor whose response largely re-iterated information already presented but did make the new argument that the recommended dosing should be 'simple and unambiguous to facilitate the treatment by health care providers. As HAE is an Orphan disease, some health care providers would only have a very few HAE patients in their entire practice to accumulate sufficient experience to individualize treatment for each patient.'

The evaluator agrees on the importance of providing suitable information for prescribers in the PI and that it would be inappropriate for an inexperienced healthcare provider to attempt to individualise treatment in HAE patients. However, in the Australian context, patients with HAE are most likely to be looked after by an immunology/allergy specialist with experience in the management of HAE and who is accustomed to individualising care. The evaluator is of the opinion that appropriate use of lanadelumab would be better ensured by the PI limiting the prescription of lanadelumab to such physicians and by the limitations to dosing information being explicit: *'Takhzyro therapy should be initiated under supervision of a physician experienced in the care of patients with HAE' and 'the optimal dose and dose frequency have not been established. The following regimens were found to have similar efficacy in the clinical trials: 150 mg every 4 weeks, 300 mg every 4 weeks and 300 mg every 2 weeks'.*



***Efficacy according to type of HAE***

Only patients with HAE with deficient or dysfunctional C1-INH (types I or II) could participate in the clinical development programme for lanadelumab, including Study DX-2930-03. Patients with type III HAE were excluded. Sub-group analysis in Study DX-2930-03, found that efficacy was demonstrated in patients with HAE type I. However, there were only 12 patients with HAE type II included in the study, limiting any conclusions regarding efficacy in this group. Therefore, efficacy has not been demonstrated in HAE type II or HAE type III.

The sponsor's proposed indication is not limited to any specific HAE types. This issue has been raised with the sponsor with respect to HAE type III. The sponsor acknowledged that the pathophysiology of HAE with normal C1-INH (formerly known as type III) is yet to be fully understood. The sponsor provided some speculations regarding the pathophysiology of HAE type III and argues that the plasma kallikrein-kinin system, with unregulated pKal and excess bradykinin is also key to this. On this basis, the sponsor argues that the 'prevention treatment effects of lanadelumab could be extrapolated to HAE with normal C1-INH'. However, the evaluator notes that it is evident from clinical guidelines, funding and regulatory bodies that HAE with normal C1-INH is not considered the same disease as HAE with deficient or dysfunctional C1-INH. Given the uncertainty around the pathophysiology of HAE with normal C1-INH (Type III), the lack of information regarding efficacy of current HAE treatments in this group due to their exclusion from pivotal Phase III studies of new treatments, the specific limiting of current guidelines to HAE types I and II and the specific limiting of approved indications of newer HAE treatments to HAE types I and II, the evaluator recommends that the indication be reworded such that the target population is limited to HAE with deficient or dysfunctional C1-INH (types I and II). The evaluator recognises that there were only a small number of patients with HAE type II included in the lanadelumab clinical studies but is of the opinion that it is reasonable to extrapolate to this group, given their similar pathophysiology and given that it is generally accepted practice to group the two types together in clinical guidelines.

***Generalisability to the Australian population***

It is not clear that the intention to treat population in the main efficacy study represents those HAE patients who would be considered for long term prophylaxis in Australia. The intention to treat population of Study DX-2930-03 represents patients with moderately severe HAE as shown by a median baseline HAE attack rate of 3 per month and 65% with a history of laryngeal attack. However, only around 55% were receiving prior long term prophylaxis. This low rate may reflect the clinical guidelines which do not provide clear criteria by which long term prophylaxis is indicated and which recognise two approaches in the management of more severe HAE; the use of long term prophylaxis or on-demand treatment alone with an emphasis on early treatment and home administration. However, it may also indicate a population whose disease severity is less than that required for long term prophylactic therapy in Australia, where the currently available options are C1-INH concentrate and danazol. For the option preferred by clinical guidelines, C1-INH concentrate, the NBA has determined that funded C1-INH concentrate for long term prophylaxis is only available for those HAE patients who have failed oral therapy and who have a baseline attack rate of 8 or more per month.

***Indirect comparison to current treatments***

In terms of efficacy in comparison to current long term prophylaxis options, C1-INH concentrate and danazol, only indirect comparison can be made. The respective PIs provide the evidence upon which TGA approvals for this indication was based. In a placebo controlled crossover study in HAE patients with a baseline attack rate of at least 2 per month, prophylactic use of Cinryze was reported to reduce HAE attacks by more than two-fold during the 12 week treatment period (mean 6.3 attacks for Cinryze versus



12.8 attacks for placebo,  $p < 0.0001$ ). A double blind study that investigated danazol for prophylaxis in 9 patients, found that HAE attacks occurred in 44 of 47 placebo courses, but only one attack occurred during 46 danazol courses. A C1-INH formulation suitable for SC administration, Haegarda, has been approved elsewhere for prophylactic use. The FDA approved label reports that a placebo controlled crossover study found that twice weekly Haegarda at 40 or 60 IU/kg reduced time-normalised HAE attacks from 3.61 to 1.19 attacks per month and 4.03 to 0.52 attacks per month respectively. Based on this information, the efficacy results achieved with lanadelumab appear comparable to those of other agents used for prophylaxis.

## Safety

### Studies providing safety data

The presentation of safety data in the Summary of Clinical Safety includes data from the four clinical studies and integrated data from the two Phase III studies. Brief descriptions of the studies are provided below.

- Study DX-2930-03: a completed double blind, placebo controlled Phase III study that enrolled 125 participants with HAE type I or II who were randomised to receive placebo ( $n = 41$ ), lanadelumab 150 mg every 4 weeks ( $n = 28$ ), lanadelumab 300 mg every 4 weeks ( $n = 29$ ) or lanadelumab 300 mg every 2 weeks ( $n = 27$ ) for a six month period.
- Study DX-2930-04: an ongoing open label Phase III study with safety data provided through to the interim cut-off date of 1 September 2017. This study has enrolled 109 rollover participants for Study DX-2930-03 and 103 non-rollover participants. All participants received lanadelumab 300 mg every 2 weeks, although this commenced after a dose-and-wait period for the rollover subjects. After administration of the first 2 doses of lanadelumab, suitable participants were offered the option of self-administration.
- Study DX-2930-01: a completed Phase I study that investigated a single dose of lanadelumab or placebo (0.1 mg/kg  $n = 6$ , 0.3 mg/kg  $n = 6$ , 1.0 mg/kg  $n = 6$ , 3.0 mg/kg  $n = 6$ , placebo  $n = 8$ ) in 32 healthy adult subjects
- Study DX-2930-02: a completed Phase I study that investigated two doses of lanadelumab or placebo two weeks apart (30 mg  $n = 4$ , 100 mg  $n = 4$ , 300 mg  $n = 5$ , 400 mg  $n = 11$ , placebo  $n = 13$ ) in adult subjects with HAE type I or II. Of the 38 participants, 19 (placebo  $n = 8$ , lanadelumab treated  $n = 11$ ) subsequently participated in Study DX-2930-04.
- Other reports related to safety. The sponsor has included five additional reports related to safety in the dossier:
  - Potential for cardiovascular effects of plasma kallikrein inhibitors: a review of the literature and of data from Study DX-2930-03
  - Lanadelumab QT evaluation plan assessment
  - ECG assessment report for Study DX-2930-03
  - ECG report for Study DX-2930-04
  - Review of lanadelumab (DX-2930) hepatic events in Phase III hereditary angioedema (HAE) prevention studies
  - Paediatric data: Lanadelumab (SHP643, DX-2930).

## Patient exposure

**Table 9: Safety population by study and dose regimen**

|   | DX-2930-03 Treatment Arms |           |           |           | DX-2930-04                   |                  |              | Total |
|---|---------------------------|-----------|-----------|-----------|------------------------------|------------------|--------------|-------|
|   | Placebo                   | 150mg Q4W | 300mg Q4W | 300mg Q2W | DX-2930-03                   |                  | Non-rollover |       |
|   |                           |           |           |           | Lanadelumab treated rollover | Placebo-rollover |              |       |
| DX-2930-03 Safety Population              | 41                        | 28        | 29        | 27        | -                            | -                | -            | 125   |
| DX-2930-04 Safety Population              | -                         | -         | -         | -         | 76                           | 33               | 103          |       |
| Integrated safety population              | 41                        | 28        | 29        | 27        | -                            | -                | 103          | 187   |
| Integrated lanadelumab-treated population | -                         | 28        | 29        | 27        | -                            | 33               | 103          | 220   |
| Integrated placebo treated population     | 41                        | -         | -         | -         | -                            | -                | -            | 41    |
| Integrated placebo-rollover population    | -                         | -         | -         | -         | -                            | 33               | -            | 33    |
| Sources: Tables 2.1-2.4, ISS, Module 5    |                           |           |           |           |                              |                  |              |       |

Analyses of the integrated safety population, the integrated lanadelumab-treated population and the integrated placebo-rollover population included safety outcomes as reported in both Study DX-2930-03 and Study DX-2930-04 for unique individuals during their participation in the relevant study.

The following rationale for the number of 'integrated safety populations' was provided:

'A focus will be placed on the analyses from Study DX-2930-03 which allow for direct evaluation of the safety of lanadelumab compared to placebo. Analyses using the lanadelumab-treated population will explore if any new safety signals emerge with longer term exposure and within patient subgroups. The placebo-rollover population will be used to explore trends in certain safety events (eg, ISR AEs) since this subset of subjects received treatment with both placebo (Study DX-2930-03) and lanadelumab (Study DX-2930-04).'

## Safety issues with the potential for major regulatory impact

### *Liver function and liver toxicity*

The sponsor has proposed that increased AST and increased ALT be described in the PI as common ( $\geq 1$  in 100 to  $< 1$  in 10) adverse reactions with lanadelumab. No monitoring of liver function during treatment is proposed.

### *Review of lanadelumab (DX-2930) hepatic events in Phase III hereditary angioedema (HAE) prevention studies*

An analysis of the adverse events (AE) of elevated liver transaminases in the integrated safety population was not provided in the Summary of Clinical Safety. Instead, an expert's review was referred to. This review is briefly summarised below.

The expert reviewed information from the non-clinical and clinical studies. The review noted that some liver abnormalities had been observed in repeat dose studies in rats, although these were considered minimal and not toxicologically significant, and that no clinically significant hepatic injury was found in studies of monkeys. In the Phase I studies, there was one healthy subject in whom a clinically significant elevation in ALT occurred. However, this occurred 84 days after the single dose of 1.0 mg/kg of lanadelumab. In the Phase Ib study, there were 3 lanadelumab exposed patients in whom ALT elevation  $> 1$  to

< 3 x upper limit of normal (ULN) during the treatment period occurred. However, these were not considered clinically significant and were not reported as AEs.

In Study DX-2930-03, the expert noted that many subjects had an underlying history of the metabolic syndrome (obesity, hepatic steatosis, diabetes, hypertension, and so on), and that there was a moderate imbalance in baseline values of ALT > 1 to < 3 x ULN between placebo and the combined lanadelumab groups (9.76% on placebo versus 21.43% on combined lanadelumab). Treatment emergent elevations in ALT > 3 x ULN were reported in 4 of 84 subjects (4.8%) receiving lanadelumab. Lanadelumab was permanently discontinued due to this in one patient.

In Study DX-2930-04, elevated ALT > 3 x ULN was reported in 6 of 212 subjects (2.8%), with one patient discontinuing from the study due to this. Brief summaries of individual cases (4 patients from Study DX-2930-03 and 7 patients from Study DX-2930-04), with the reviewer's assessment, were provided. These included patients with transaminase elevation and one patient with mildly elevated ALP.

The expert's assessments were that:

- Transaminase elevation was due to pre-existing liver or biliary disease or concomitant medications in 6 patients. There was one subject in whom the transaminase elevation was attributed to muscle injury (surfing accident with concussion).
- Possible 'drug tolerance' where transaminase elevation occurred but then declined during ongoing treatment) was identified in 2 patients. In another patient, transaminase elevation resulted in lanadelumab being withheld for 80 days, during which time the transaminases normalised. There was no recurrence in transaminase elevation on recommencement of lanadelumab.
- There was one patient in whom possible drug induced liver injury from lanadelumab was identified due to mild asymptomatic ALT elevation at 4 months with slow improvement on permanent discontinuation and no suspect concomitant medications or other causes identified.

The expert concluded that:

- Lanadelumab was associated with asymptomatic, reversible, mild-moderate ALT/AST elevations with a latency of 1 to 6 months; the incidence appears to be < 5% of subjects.
- There was evidence for drug tolerance (adaptation) and that this seemed to be the most common course. Negative rechallenge responses have been seen when the investigational product has been paused and restarted.
- There were no signs of hypersensitivity reactions.
- There were no Hy's Law cases;<sup>26</sup> cases of acute liver failure or Grade 4 ALT/AST elevations.
- There was no correlation of ALT/AST elevations to plasma concentrations.
- There was no antidrug antibody formation for all 10 subjects.

The following recommendation regarding transaminase monitoring was made:

'Routine ALT monitoring seems unnecessary as the injury is mild and reversible despite continuing lanadelumab, and negative rechallenge responses were seen after restarting the drug following prolonged periods where it was being held.'

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<sup>26</sup> Hy's law = evidence of acute liver injury with ALT or AST >3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN, with liver injury not primarily cholestatic and not caused by disease but by drug.

The evaluator agrees with the assessment for the individual patients according to the information provided and that there were no reports of Hy's Law cases or acute liver failure. The expert provided no speculation as to the possible mechanism of drug-induced liver injury. The recommendation regarding monitoring is discussed further below.

#### Study DX-2930-03

According to the CSR, most participants had normal AST and ALT at baseline. There were 4 placebo treated subjects with baseline elevated ALT (1 to < 3 x ULN) and 2 with elevated AST (1 to < 3 x ULN). There were 20 lanadelumab treated subjects with baseline elevated ALT (1 to < 3 x ULN n = 18 and 3 to 5 x ULN n = 2) and 9 with elevated AST (1 to < 3 x ULN).

Changes from Baseline were as follows:

- ALT increase from Baseline: There were 6 subjects in the placebo arm in whom an increase from baseline in ALT level to 1 to < 3 x ULN was reported; there were 24 lanadelumab treated subjects in whom an increase from baseline in ALT level was reported (1 to < 3 x ULN, n = 20; 3 to 5 x ULN, n = 3; > 5 x ULN, n = 1). There were 6 lanadelumab treated subjects in whom the ALT level was normal during treatment despite elevated baseline levels.
- AST increase from Baseline: There were 3 subjects in the placebo arm in whom an increase from baseline in AST level to 1 to < 3 x ULN was reported; there were 9 lanadelumab treated subjects in whom an increase from baseline in AST level was reported (1 to < 3 x ULN, n = 9; 3 to 5 x ULN, n = 1; > 5 x ULN, n = 1).
- ALP increase from Baseline: There were 2 placebo subjects with an increase in ALP (1 to < 3 x ULN, n = 1, 3 to 5 x ULN, n = 1). There were 6 lanadelumab treated subjects in whom an increase in ALP from baseline to 1 to < 3 x ULN was reported.
- Bilirubin: there were no participants in whom there was an increase from Baseline of > 2 x ULN.

According to the CSR, there were 3 of 84 (3.6%) lanadelumab treated subjects in whom the ALT level increased to 3 to 5 x ULN (2 subjects) or > 5 x ULN (1 subject) and 1 subject (1.2%) in whom there was no change from the baseline elevated ALT level of 3 to 5 x ULN. There were 2 of 84 (2.4%) lanadelumab treated subjects in whom the AST level increased to > 3 x ULN from the baseline.

A post hoc eDish (evaluation of Drug-induced Serious Hepatotoxicity) plot was performed. This identified four subjects in the Temple's Corollary quadrant ([information redacted] in the lanadelumab 150 mg q4wks arm, [information redacted] in the lanadelumab 300 mg q4wks arm, [information redacted] in 300 mg q4wks group, and [information redacted] in the lanadelumab 300 mg q2wks arm). There were no subjects identified in the Hy's Law quadrant.

Brief narratives were provided for the 4 subjects appearing on the eDISH plot. These subjects were also assessed in the expert's review.

Summaries of the narratives as provided in the CSR and expert's review were provided. According to the expert's review, of the 4 participants in whom an increase in ALT was reported, one subject discontinued from the study and three subjects continued without dose interruption or modification.

#### Study DX-2930-04

Liver-related biochemistry abnormalities were observed at baseline: 28/212 (13.2%) of all subjects had 1 to 3 x ULN ALT pre-treatment; 1 subject had > 5 x ULN.

The CSR identified the following increases in ALT, AST and bilirubin during treatment through shift tables:

- ALT pre-treatment  $\leq 1 \times \text{ULN}$  or 1 to 3  $\times \text{ULN}$  to post-treatment 1 to  $< 5 \times \text{ULN}$  or  $> 5 \times \text{ULN}$ : 5 subjects
- AST pre-treatment  $\leq 1 \times \text{ULN}$  or 1 to 3  $\times \text{ULN}$  to post-treatment 1 to  $< 5 \times \text{ULN}$  or  $> 5 \times \text{ULN}$ : 6 subjects
- Bilirubin pre-treatment  $\leq 2 \times \text{ULN}$  to post-treatment  $> 2 \times \text{ULN}$ : 1 subject.

Liver-related biochemical tests that were associated with AEs were consistent with the variables identified in the shift tables. There were 4 subjects in whom liver function test (LFT) abnormalities were reported as severe treatment emergent adverse events (TEAE): ALT increased (3 subjects), AST increased (2 subjects), and Hepatic enzyme increased (1 subject). The subjects by DX-2930-04 ID number were: [Information redacted].

An eDISH analysis was performed. This analysis identified no Hy's Law cases but did identify one subject in the Cholestasis quadrant [information redacted] and 6 subjects in the Temple's Corollary quadrant [information redacted]. These included the 4 subjects in whom severe AEs had been reported.

Brief narratives were provided for the 7 subjects appearing on the eDISH plot. These subjects were also assessed in the expert's review, together with one additional subject.

All elevations were asymptomatic, with no associated hyperbilirubinemia or elevated ALP. One subject discontinued the study due to an elevated baseline value (ALT/AST  $> 3 \times \text{ULN}$ ). In one subject, lanadelumab was paused and then restarted with no subsequent increase in transaminase levels. There were 2 other subjects in whom the transaminase elevations occurred during the 'dose and wait' period. These subjects continued into the regular dosing regimen as planned. In 5 of the 6 cases, the transaminase elevation was transient. In the 6th subject, although ALT decreased, the value remained  $> 3 \times \text{ULN}$  at the time of the interim report. A liver biopsy performed on that patient revealed Grade 2 to 3 steatohepatitis with Stage 3 to 4 fibrosis consistent with moderate to severe hepatosteatosis with incomplete cirrhosis, suggestive of pre-existing chronic liver disease.

#### Other studies

##### *Study DX-2930-01*

There was one lanadelumab treated subject in whom elevated alanine aminotransferase was reported on Day 84 after a single dose on 1.0mg/kg. The ALT level was 217 U/L (reference range  $< 38 \text{ U/L}$ ) and graded as toxicity grade 3. The event was reported as a TEAE of liver function test abnormal. On the same day, other liver function tests were also abnormal, with elevated AST (68 U/L, reference range  $< 45$ ); elevated gamma glutamyl transaminase (210 U/L (reference range 9 to 40 U/L)) and elevated ALP (128 U/L, (reference range 46 to 108)). However, bilirubin, prothrombin time and albumin were all within normal limits. The patient was lost to follow-up so the outcome is unknown. According to the expert's review, the abnormalities were attributed to alcohol by the investigator. The expert did not consider this likely to be due to lanadelumab given the time between the dose and the event.

##### *Study DX-2930-02*

According to the expert's review, 'there were 6 subjects with ALT  $> 1$  to  $< 3 \times \text{ULN}$  during the treatment period in the 100 mg (n = 1), 300 mg (n = 1), 400 mg (n = 1) and placebo (n = 3). One additional placebo subject had an elevated ALT  $> 3 \times \text{ULN}$ '. These events are not discussed in the CSR or Summary of Clinical Safety as these discussions were limited to laboratory abnormalities that were reported as AEs and 'laboratory abnormalities generally were not considered AEs unless they were associated with clinical signs or symptoms or required medical intervention'.

### *Evaluator conclusions regarding hepatotoxicity*

The evaluator agrees that, to date, lanadelumab appears to have only been associated with mild and reversible transaminase elevation and accepts the expert's assessment that this occurs in around 5% of patients and the sponsor's assessment that it is "common". However, the evaluator is concerned that the full spectrum of liver injury that may occur with lanadelumab may yet to be observed, given that only 257 people in total have been exposed to lanadelumab. The evaluator also notes that of the 10 patients with elevated transaminases in Studies DX-2930-03 and DX-2930-04 who were discussed in the review:

- 4 permanently discontinued treatment, with this due to the elevated transaminases in 2 of 4; due to a different AE in one and due to not meeting inclusion criteria in the fourth.
- there were only 2 cases in which lanadelumab was temporarily withheld and then recommenced. In both patients there was no recurrence of transaminase elevation (negative rechallenge)
- there were 4 patients in whom lanadelumab treatment was continued without interruption. In two of these patients, the transaminase levels normalised. In the other two, the transaminase levels remained persistently elevated but did not substantially worsen.

The evaluator considers that these varying approaches to management (discontinuation permanently, temporarily or continued without interruption) make it difficult to be certain of what may be the 'natural history' of lanadelumab induced liver abnormalities and that the expert's conclusion that 'the injury is mild and reversible' with no need for monitoring during treatment may be overly optimistic. Given the uncertainties, the evaluator recommends a more conservative approach to monitoring with repeat liver function tests at 2 and 6 months and that there should be a description of the hepatic events, and their management, as occurred in the clinical studies, in the PI.

### ***Renal function and renal toxicity***

No events suggestive of renal toxicity were reported in the clinical studies.

### ***Haematology and haematological toxicity***

No events suggestive of haematological toxicity were reported in the clinical studies.

### ***Serious skin reactions***

Localised skin reactions (ISRs) were common in both lanadelumab and placebo treated HAE patients, although the incidence was higher in the lanadelumab treated patients in Study DX-2930-03. However, generalised skin reactions were uncommon and did not occur more frequently in lanadelumab treated patients (the preferred term 'rash' was reported in 2 of 41 placebo subjects and 4 of 84 in lanadelumab treated subjects in Study DX-2930-03). There were no reported cases of photosensitivity, erythema multiforme, Stevens' Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis in the clinical studies.

### ***Rhabdomyolysis***

Muscle injury is a potential concern with lanadelumab treatment. Elevated creatinine kinase has been reported in a number of lanadelumab treated subjects and myalgia is included as a common adverse reaction in the draft PI. According to the RMP, myalgia is not associated to a relevant risk. Muscle injury, creatinine kinase elevation and myalgia were not discussed in the sponsor's Summary of Clinical Safety.

In Study DX-2930-01, in healthy subjects receiving a single dose of lanadelumab, there were three events of elevated creatinine phosphokinase (one in a subject receiving

0.1mg/kg lanadelumab, one in a subject receiving 3.0 mg/kg lanadelumab and one event in a subject receiving placebo):

- one subject in the 0.1 mg/kg group had a creatinine phosphokinase level of 902 U/L (reference range 21 to 215 U/L) on Day 21. The subject had normal creatinine phosphokinase values on Day 28, Day 42, and Day 56. This subject also had milder creatinine phosphokinase elevations on Day 84 (272 U/L; toxicity grade 1) and Day 112 (345 U/L; toxicity grade 2). This was considered to be related to study drug by the investigator.
- One subject receiving 3.0mg/kg lanadelumab had an elevated creatinine phosphokinase of 2,179 U/L (reference range 21 to 215 U/L) on Day 42. This elevation resolved by Day 56 and the subject was noted to be a fitness instructor with strenuous activity. This was not considered related to study drug.
- The subject in the placebo group had a creatinine phosphokinase level of 1,967 U/L (reference range 32 to 294 U/L) on Day 42. This subject also had milder creatinine phosphokinase elevations on Day 7 (299 U/L), Day 21 (299 U/L), Day 28 (304 U/L), Day 56 (304 U/L), and Day 112 (341 U/L). No toxicity grade was provided for any of these milder creatinine phosphokinase elevations. This was considered to be related to study drug by the investigator.

None of the creatinine phosphokinase elevations were associated with myalgia or muscle weakness.

In Study DX-2930-04, there were two patients in whom lanadelumab treatment was ceased or temporarily interrupted due to elevated transaminases in association with elevated creatinine kinase:

- One patient had a creatinine phosphokinase level of > 22,000, in association with elevated transaminase, 22 days after the third and last dose of lanadelumab. Treatment had been ceased due to marked transaminase elevations with ALT 681 and AST 201 prior to the third dose. A creatinine kinase result at this time was not provided. The transaminase and creatinine kinase elevations were attributed to muscular injury and the subject's history of strenuous exercise was noted. No further information regarding the strenuous exercise was provided.
- One patient had lanadelumab treatment interrupted on two occasions: once on Day 127 due to elevated ALT and one month later, on Day 155, due to elevated creatinine phosphokinase and elevated AST. These events were reported as moderate severity AEs that were 'not related'.

In the Study DX-2930-04 CSR, there were a total of 6 participants in whom elevated creatinine phosphokinase were reported as AEs. These were graded as mild in 3 participants and moderate in 3 participants. No other information regarding these events could be readily located by the evaluator.

In Study DX-2930-03, there were no patients in whom elevated creatinine phosphokinase was reported as an AE. In Study DX-2930-02, there were no patients in whom elevated creatinine phosphokinase was reported as an AE.

Both AST and ALT may be released from damaged muscle. This, rather than hepatotoxicity, may account for the elevations observed in association with elevated creatinine phosphokinase in the 2 patients above. A relationship between elevated creatinine kinase and lanadelumab cannot be excluded on the information provided. Pending further information from the sponsor, the possible adverse effect of myositis/rhabdomyolysis should be included in the RMP and PI.

## Other safety factors of possible regulatory importance

### Self-administration

Subcutaneous administration into the abdomen, thigh, or upper arm by the patient, care giver or healthcare professional is proposed in the draft PI. This is consistent with clinical guidelines that emphasise early treatment of acute attacks by self-administration of parenteral therapies.

In Studies DX-2930-01, DX-2930-02 and DX-2930-03, all administration was by study site personnel. In Study DX-2930-04, administration was by study site personnel for the first two doses. Suitable participants, or carers, were provided with the option of self-administration (at home or in the clinic) after the first two doses. Training was provided by site personnel and the body location for administration could be upper arm, thigh or abdomen.

As self-administration by HAE patients may result in a higher incidence of injection site reactions, an analysis of injection site reactions in Study DX-2930-04 according to type of administration (self-administration at home, self-administration in clinic and study staff in clinic) was performed. The results are presented in the Summary of Clinical Safety and Clinical Overview. The event rate per dose was calculated to allow for comparison given the difference in the number of administrations in each group. The injection site reaction event rate was similar across the groups.

**Table 10: Study DX-2930-04: Summary of injection site reactions by type of administration**

| Subject performing or receiving administration type<br>Category | All Subjects Overall (N=212) |                               |                            |
|---|------------------------------|-------------------------------|----------------------------|
|   | Self-administration at Home  | Self-administration at Clinic | Study Staff Administration |
|   | N=106<br>n (%) m             | N=146<br>n (%) m              | N=204<br>n (%) m           |
| Total Number of Doses <sup>a</sup>                              | 655                          | 1127                          | 1375                       |
| Mean Number of Doses  | 6.2                          | 7.7                           | 6.7                        |
| Any ISR TEAE  | 0.299                        | 0.218                         | 0.255                      |
| Any Related ISR TEAE  | 0.278                        | 0.209                         | 0.199                      |
| Any Serious ISR TEAE  | 0                            | 0                             | 0                          |
| Any Related Serious ISR TEAE                                    | 0                            | 0                             | 0                          |
| Any Severe ISR TEAE   | 0                            | 0                             | 0                          |
| Any Related Severe ISR TEAE                                     | 0                            | 0                             | 0                          |
| Any Investigator-reported AESI                                  | 0                            | 0.003                         | 0.002                      |
| Deaths due to ISR TEAE  | 0                            | 0                             | 0                          |
| Hospitalizations due to ISR TEAE                                | 0                            | 0                             | 0                          |
| Discontinuation due to ISR TEAE                                 | 0                            | 0                             | 0                          |

AESI=adverse event of special interest; ISR=injection-site reaction; m=number of events per study drug administration of the corresponding type; TEAE=treatment-emergent adverse event

Percentages are based on the number of subjects performing the corresponding administration type.

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

Related TEAEs are TEAEs classified as related to study drug by the investigator.

Severe TEAEs are TEAEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.

<sup>a</sup> The total number of doses that were administered using the corresponding administration type.

The median duration of all injection site reactions was 0.03 hours (range: 0 to 81.5) for self-administered doses at home, 0.07 hours (range: 0 to 94.7) for self-administered doses in-clinic, and 0.10 hours (range: 0 to 662.5) for study staff administration in-clinic. Regardless of administration type, the majority of injection site reactions were ≤ 0.5 hour duration.



The anatomical site where the injection occurred was generally different for self-administration versus study staff and was identified as a potential confounding factor in the analysis. Study staff generally administered lanadelumab in the arm, whereas this site is awkward for subjects who are self-administering; therefore, the majority of self-administered doses occurred in the abdomen.

Self-administration by trained patients/carers did not appear to increase the incidence of injection site reactions. Other potential complications of administration by patients/carers such as localised or systemic infection, needle-stick injuries, inadvertent intravascular or intramuscular injection were not discussed in the sponsor's documents. The evaluator could find no reports of such events as AEs in the clinical study report of Study DX-2930-04.

The sponsor's draft PI includes the statement that 'Takhzyro is intended for self-administration or administration by a caregiver. The patient or caregiver should be trained on subcutaneous injection technique by a healthcare professional'. There is no reference to potential risks associated with self-administration, noting that safety with wider use of this practise may differ from that observed in the closely monitored clinical trial setting. Detailed instructions for self-administration are provided in the CMI but not in the PI; this may prevent training being provided that closely matches the detailed instructions in the CMI and may create confusion during self-administration, with increased risk. The evaluator has proposed that the PI includes a description of potential risks and that the PI include the same administration instructions as the CMI.

***Safety with recommencement after a period of no treatment or transition from other long term prophylaxis***

As noted in the Clinical Overview, there were several situations in the Phase III studies that could create interruptions in lanadelumab treatment, involve transitions from 1 regimen to another, or involve the concomitant use of rescue medications.

**Interruptions:**

- Participation in Study DX-2930-02 followed by enrolment in Study DX-2930-04 (as non-rollovers): 11 lanadelumab-treated subjects
- Participation in Study DX-2930-03 followed by enrolment in Study DX-2930-04 (as rollovers), which involved a 'dose-and-wait' stage during the treatment period for all subjects: 76 subjects. These patients could also experience an increase in the total monthly dose and frequency of lanadelumab when participating in Study DX-2930-04
- Having experienced a treatment emergent adverse event that resulted in temporary interruption in study treatment: 1 subject in Study DX-2930-03 and 5 subjects in Study DX-2930-04

In relation to the rollover patients entering Study DX-2930-04 who had previously received lanadelumab, the CSR provides an estimated percentage of around 30% in whom the dose-and-wait period lasted more than 10 weeks. AEs according to stage in the extension study and treatment arm in Study DX-2930-03 were shown in Table 11. This found that the proportion of subjects in whom any treatment emergent AEs were reported was lower in the dose-and-wait phase (44% to 57.6%) compared to the regular dosing stage (64 to 77%) for each DX-2930-03 treatment arm except for the 300 mg every 2 weeks arm (treatment emergent AE rate 76% in the dose-and-wait phase and 72% in the regular dosing stage). The incidence of anti-drug antibodies was higher in rollover patients (11%) compared to non-rollover subjects (6.8%).

**Table 11: Treatment-emergent adverse events (excluding HAE attack reported events) during the treatment period by System Organ Class and Preferred Term (rollover safety population)**

| Time Period<br>System Organ<br>Class<br>Preferred Term        | Placebo<br>N=33<br>n (%) m | Lanadelumab<br>150 mg | Lanadelumab<br>300 mg | Lanadelumab<br>300 mg | Total<br>N=109 |
|---|----------------------------|-----------------------|-----------------------|-----------------------|----------------|
|   |                            | q4w                   | q4w                   | q2wks                 |                |
|   |                            | N=26                  | N=25                  | N=25                  |                |
|   |                            | n (%) m               | n (%) m               | n (%) m               | n (%) m        |
| <i>Treatment Period</i>                                       |                            |                       |                       |                       |                |
| -- Any TEAE   | 27 (81.8) 204              | 23 (88.5) 267         | 21 (84.0) 107         | 24 (96.0) 182         | 95 (87.2) 760  |
| <i>Dose and Wait Stage of the Treatment Period</i>            |                            |                       |                       |                       |                |
| -- Any TEAE   | 19 (57.6) 35               | 14 (53.8) 40          | 11 (44.0) 25          | 19 (76.0) 53          | 63 (57.8) 153  |
| <i>Regular Dosing Stage of the Treatment Period</i>           |                            |                       |                       |                       |                |
| -- Any TEAE   | 25 (75.8) 161              | 20 (76.9) 222         | 16 (64.0) 80          | 18 (72.0) 128         | 79 (72.5) 591  |
| -- General disorders<br>and administration<br>site conditions | 14 (42.4) 79               | 13 (50.0) 145         | 7 (28.0) 29           | 6 (24.0) 72           | 40 (36.7) 325  |

There was some information regarding the development of anti-drug antibodies in patients who participated in Study DX-2930-02 and who then, some 2 years later, participated in Study DX-2930-04. This has been discussed, with there being no signal for an increase in anti-drug antibody development in these patients. Safety in these patients was not otherwise discussed.

#### Transitions

In Study DX-2930-04, subjects who were receiving a long term prophylaxis regimen prior to entering the study, were to taper off their regimen over a period of up to 3 weeks at the start of the lanadelumab treatment period. Therefore, during this period, they received both a background of long term prophylaxis therapy and lanadelumab treatment. Of the 103 non-rollover subjects, 63 (61.2%) tapered off of long term prophylaxis in Study DX-2930-04, the majority had a history of long term prophylaxis with C1-INH only (53 (51.5%) subjects); a few subjects had received oral therapy (8 (7.8%)) or both C1-INH and oral therapy (2 [1.9%]).

In relation to AEs reported during the tapering period in Study DX-2930-04, the Clinical Overview reports that of the 63 non-rollover subjects who had been on long term prophylaxis, only 33 had a nonzero tapering period during which both the prior long term prophylaxis and lanadelumab was received. For these 33 patients, 'the AE profile observed over the limited duration of the tapering period was overall positive, with rates lower than those observed during the much lengthier non-tapering period'.

It is difficult to draw any firm conclusion on the limited information provided and the small number of patients involved. However, there is no apparent safety signal with recommencing regular lanadelumab treatment after an interruption of several weeks to 2 years. There also does not appear to be a safety signal with the co-administration of lanadelumab whilst tapering currently available long term prophylaxis.

#### Long-term safety

According to the sponsor, 'at the time of the Study DX-2930-04 interim clinical study report, 75 subjects had at least 1 year of cumulative study experience with lanadelumab, including their experience on Study DX-2930-03 and Study DX-2930-04. Of the 75, 70 were rollover patients from Study DX-2930-03'.

The 12 months of cumulative study experience in the rollover patients included the dose and wait period. As noted above, this was more than 10 weeks in many rollover patients. The sponsor was asked for the number of rollover patients with 12 months of cumulative lanadelumab treatment (that is, study experience exclusive of the dose-and-wait period).

According to the sponsor's response, there were 52 rollover patients with cumulative exposure of 12 months, making a total of 57 patients with cumulative exposure of 12 months.

The sponsor stated that 'the safety profile for lanadelumab treated rollover subjects with up to 12 months of exposure was consistent with the profile observed through 6 months of treatment in pivotal, placebo controlled trial.'

A summary of TEAEs by duration of exposure in the integrated safety population of lanadelumab treated subjects was presented in Table 12.

**Table 12: Lanadelumab treated population: Summary of treatment emergent AEs (excluding HAE attack reported events) by duration of exposure**

| Category                                  | Lanadelumab-Treated Population (N=220) |                           |                            |                                       |
|---|--|---------------------------|----------------------------|---------------------------------------|
|   | First 3 months<br>n (%) m              | First 6 months<br>n (%) m | First 12 months<br>n (%) m | Entire Treatment<br>Period<br>n (%) m |
| Overall Subject-time (years)              | 50.3                                   | 106.8                     | 160.2                      | 174.8                                 |
| Average Subject-time (years)              | 0.23                                   | 0.49                      | 0.73                       | 0.79                                  |
| Total Number of Doses                     | 1253                                   | 2702                      | 3834                       | 4216                                  |
| Average Number of Doses                   | 5.7                                    | 12.3                      | 17.4                       | 19.2                                  |
| Any TEAE                                  | 170 (77.3) 777                         | 188 (85.5) 1515           | 196 (89.1) 2075            | 196 (89.1) 2220                       |
| Any Related TEAE                          | 101 (45.9) 422                         | 112 (50.9) 835            | 118 (53.6) 1063            | 118 (53.6) 1134                       |
| Any Serious TEAE                          | 5 (2.3) 6                              | 7 (3.2) 9                 | 11 (5.0) 15                | 11 (5.0) 15                           |
| Any Related Serious TEAE                  | 0                                      | 0                         | 0                          | 0                                     |
| Any Severe TEAE                           | 9 (4.1) 14                             | 21 (9.5) 28               | 27 (12.3) 36               | 27 (12.3) 38                          |
| Any Related Severe TEAE                   | 3 (1.4) 5                              | 4 (1.8) 7                 | 4 (1.8) 7                  | 4 (1.8) 7                             |
| Any Investigator-reported AESI            | 9 (4.1) 13                             | 11 (5.0) 15               | 12 (5.5) 20                | 12 (5.5) 21                           |
| Deaths due to TEAE                        | 0                                      | 0                         | 0                          | 0                                     |
| Hospitalizations due to TEAE <sup>a</sup> | 5 (2.3) 6                              | 7 (3.2) 9                 | 11 (5.0) 15                | 11 (5.0) 15                           |
| Discontinuation due to TEAE               | 4 (1.8) -                              | 5 (2.3) -                 | 6 (2.7) -                  | 6 (2.7) -                             |

Abbreviations: AESI=adverse event of special interest; HAE=hereditary angioedema; n=number of subjects experiencing the event; m=number of events; TEAE=treatment-emergent adverse event.

Subjects were counted once per category per treatment.

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

Related TEAEs are TEAEs classified as related to study drug by the investigator.

Severe TEAEs are TEAEs classified as severe (grade 3) or life threatening (grade 4) by the investigator.

Non-HAE attack reported AEs include the subset of AEs identified in EDC as not a reported HAE attack.

<sup>a</sup> Hospitalizations were due to SAEs.

Long term safety of lanadelumab has not been established. It appears that only 57 patients have had cumulative exposure of 12 months or more. The sponsor has also not provided a clear comparison of safety between patients with exposure of 12 months or longer and patients with lesser duration of exposure. The above summary of treatment emergent AEs by duration of exposure does not show the number of subjects in each exposure group. It is notable that in this summary, the proportion for each of the categories of treatment emergent AEs shown increases progressively with the duration of treatment.

The evaluator notes that the ICH 'Note for Guidance regarding proposed long-term treatment';<sup>27</sup> recommends that '100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use.' The TGA-adopted 1987 guidance states that for the investigation of long-term safety, "The total clinical experience must generally include data on a large and representative group of patients (for example, 100) exposed to the substance for at least 12 months, irrespective of the indications." The sponsor's clinical development programme has not met this recommendation of a minimum of 100 patients treated for one year. Given the rarity and potentially life-threatening nature of the condition, this may not prevent approval. However, robust post-marketing measures would be required.

### ***Safety in special populations***

There are no specific studies that investigate safety in special populations.

According to the sponsor, exploratory subgroup analyses were performed for the Study DX-2930-03 safety population, Study DX-2930-04 safety population, and the lanadelumab treated population for summaries of AEs, related AEs, and severe AEs.

Analyses for the following sub-groups were provided in Study DX-2930-03:

- Age Group < 18 years (n = 10), 18 to < 40 years (n = 45), 40 to < 65 years (n = 65), ≥ 65 years (n = 5)
- Sex - Female (n = 88), Male (n = 37)
- Race - White (n = 113, Other (n = 12)
- Weight < 50 kg (n = 3), 50 to < 75 kg (n = 59), 75 to < 100 kg (n = 42), ≥ 100 kg (n = 21)

The distribution of subjects according to treatment arm for some of these the analyses are shown below.

**Table 13: Study DX-2930-03: Number of subjects according to sub-group**

| Sub-group              | Placebo | 150mg Q4W | 300mg Q4W | 300mg Q2W | All lanadelumab |
|------------------------|---------|-----------|-----------|-----------|-----------------|
| Age                    |         |           |           |           |                 |
| <18 years (N=10)       | 4       | 1         | 3         | 2         | 6               |
| 18 to <40 years (N=45) | 14      | 9         | 10        | 12        | 31              |
| 40 to <65 years (N=65) | 21      | 15        | 16        | 13        | 44              |
| ≥65 years (N=5)        | 2       | 3         | 0         | 0         | 3               |
| Sex                    |         |           |           |           |                 |
| Female (N=88)          | 34      | 20        | 19        | 15        | 54              |
| Male (N=37)            | 7       | 8         | 10        | 12        | 30              |
| Race                   |         |           |           |           |                 |
| White (N=113)          | 39      | 25        | 23        | 26        | 74              |
| Race: Other (N=12)     | 2       | 3         | 6         | 1         | 10              |

Source: Study DX-2930-03 CSR, Table 14.3.1.1.2

The Clinical Overview and the Summary of Clinical Safety state that: "In general, the trends in the incidence of treatment emergent AEs across the defined categories for each subgroup were similar to trends observed for all subjects overall. In some cases, differences were difficult to interpret due to low sample sizes."

<sup>27</sup> ICH Topic E 1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety For Drugs Intended For Long-Term Treatment Of Non-Life-Threatening Conditions ICH Harmonised Tripartite Guideline (CPMP/ICH/375/95)

**Comment:** The Summary of Clinical Safety refers to a number of tables to support the statement quoted above. Each of these tables provides a summary according to treatment emergent AE categories but does not indicate the number of subjects in the sub-group. Comparison across subgroups is not easy as each sub-group is presented in a separate table (for example, each age group has a separate table, each weight category has a separate table). The evaluator was unable to determine if the analyses in these tables showed similar trends in AEs across the sub-groups.

The evaluator considers that these sub-group analyses are largely meaningless due to small sample sizes and that safety in the sub-groups of age < 18, age ≥ 65 years, races other than white, weight < 50 kg and weight > 100 kg is not established by the data from the placebo controlled phase III study.

### ***Pregnancy and lactation***

According to the Summary of Clinical Safety, 3 subjects [information redacted] became pregnant during participation of Study DX-2930-04. Each of these subjects was a rollover subject from Study DX-2930-03. All 3 subjects discontinued treatment with lanadelumab upon receipt of positive serum/urine pregnancy test. One subject has since delivered a healthy infant with no issues or concerns reported. The other 2 pregnancies are ongoing, and at the time of the report, neither had experienced any complication with their pregnancy. The cumulative exposure in these subjects is shown below.

**Table 14: Cumulative lanadelumab exposure in subjects who became pregnant**

| Subject IDs in DX-2930-03/DX-2930-04 | Doses in Study DX-2930-03 | Doses in Study DX-2930-04 | Cumulative Dose |
|--------------------------------------|---------------------------|---------------------------|-----------------|
|                                      | 7 x 150 mg                | 19 x 300 mg               | 6750 mg         |
|                                      | 7 x 150 mg                | 17 x 300 mg               | 6150 mg         |
|                                      | 7 x 300 mg                | 1 x 300 mg                | 2400 mg         |

### ***Nonclinical studies***

An enhanced pre- and post-natal developmental (ePPND) study in cynomolgus monkeys was reported to not indicate adverse effects of lanadelumab on embryo-foetal development. Pharmacokinetic data from this study found the excretion of lanadelumab in the milk of lactating monkeys to be approximately 0.2% of the maternal serum level.

### ***Paediatric data***

**Comment:** the sponsor has provided a Paediatric Report that collates information regarding participants aged 12 to 17 years from Studies DX-2930-03 and DX-2930-04. The report presents safety separately for each of the two Phase III studies. There were no adolescents included in the two Phase I studies.

#### ***Study DX-2930-03***

This study included 10 patients aged 12 to 17 years, of whom 4 received placebo and 6 received lanadelumab (150 mg every 4 weeks n = 1, 300 mg every 4 weeks n = 3, 300 mg every 2 weeks n = 2). All 6 lanadelumab treated patients completed the study, with 26 weeks of exposure to lanadelumab. One subject in the 300 mg every 4 weeks group received 11 of 13 planned doses.

There were no deaths or discontinuations due to AEs amongst the adolescent patients. There was one patient in whom an SAE was reported.

The AEs reported in the adolescent participants were as follows (Note: AEs by preferred term were only reported for those that occurred in at least 2 lanadelumab treated patients):



- Placebo group
  - 2 of the 4 placebo patients experienced 6 AEs, none of which were severe or serious or required hospitalisation.
  - The reported AEs by PT were: injection site erythema (n = 1); sensation of foreign body (n = 1); rash (2 events in one patient)
- Lanadelumab treated group
  - 5 of the 6 lanadelumab treated patients experienced 30 AEs
  - One patient had on AE that was considered serious (SAE), severe and that required hospitalisation. This was a catheter port infection and required port removal.
  - The reported AEs by PT were: injection site pain (n = 3); pyrexia (n = 1), pharyngitis (n = 1); pharyngitis streptococcal (n = 1); upper respiratory tract infection (n = 1); rash (3 events in 2 patients); pruritus (n = 1).

In one placebo patient, one event was considered to be related to treatment. There were 3 lanadelumab treated patients, in whom there were 13 AEs that were considered to be related to treatment. The most common treatment related AE was injection site pain (n = 3). One lanadelumab treated subject had injection site discomfort on 10 occasions.

No adolescent had a shift to  $> 3 \times$  ULN for alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) values relative to the pre-treatment or baseline. There were two reports of a significant change from baseline in laboratory evaluations:

- activated prothrombin time shift from normal pre-treatment to  $> 1.5 \times$  ULN
- prothrombin time shift from normal pre-treatment to  $> 1.5 \times$  ULN post-treatment

One 12 year old lanadelumab treated patient had a transient anti-drug antibody positive test of low titre and not neutralising. This had no apparent clinical consequence.

#### *Study DX-2930-04*

There were 23 adolescents who participated in this ongoing study, including 9 patients who rolled over from Study DX-2930-03. The duration of therapy at the time of the interim report ranged from 5 to 12 months for the non-rollover subjects and from 7 to 11 months for the rollover subjects. If the time in Study DX-2930-03 is included, all 8 rollover patients had had longer than 12 months of study participation (range 13 to 17 months). This period of time is inclusive of the dose-and-wait period; the period of lanadelumab treatment may be some months less.

There were no deaths, SAEs, severe AEs, hospitalisations or discontinuations due to AEs amongst the adolescent patients in this study. There were 91 AEs reported in 18 of the 21 patients. The most frequently reported AEs were related to the injections site (pain, erythema, bruising; 68 events in 8 patients). See also Table 15.

**Table 15: Study DX-2930-04: Frequently reported adverse events ( $\geq 2$  lanadelumab treated Subjects aged 12 to  $< 18$  years overall excluding HAE attack reported events) by preferred term during the Treatment Period (Days 0 to 910)**

| PT  | Number of events | Number of patients |
|---|------------------|--------------------|
| Any AE  | 23               | 18                 |
| AE related to the injection site  | 68               | 8                  |
| pain  | 56               | 9                  |
| erythema, bruising, swelling  | 12               | 3                  |
| Viral upper respiratory tract infection, upper respiratory tract infection, influenza | 5                | 5                  |

| PT                                   | Number of events | Number of patients |
|--------------------------------------|------------------|--------------------|
| Abdominal pain, abdominal pain upper | 3                | 3                  |
| Headache                             | 2                | 2                  |
| Pharyngitis streptococcal            | 2                | 2                  |
| Facial pain                          | 1                | 1                  |

There were 65 AEs that were considered related to treatment. Those most commonly reported were injection site reactions, with 8 subjects reporting 51 events of injection site pain. There was also one subject with 6 events of injection site bruising.

No adolescent subject had a shift to  $> 3 \times$  ULN for alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) values relative to the pre-treatment or baseline. There were 3 reports of significant shifts from baseline in other laboratory evaluations:

- One rollover subject had their neutrophils test value shift from normal pre-treatment period value to a low neutrophils values ( $< 0.5 \times$  lower limit of normal) during the treatment period. There were no associated AEs reported in this patient.
- Two subjects had aPTT shift from normal range in the pre-treatment period to  $> 1.5 \times$  ULN post treatment.

In the testing for anti-drug antibodies, there were two subjects with positive results:

- One 13 year old rollover subject from the placebo arm in Study DX-2930-03 was positive for anti-drug antibodies at Treatment Visit 14. The anti-drug antibodies response observed was transient, was of a low titre, and tested negative for neutralising antibody. The subject was not positive for anti-drug antibodies in Study DX-2930-03.
- One 12 year old rollover subject who was also positive for low titre anti-drug antibodies on 1 unscheduled visit in Study DX-2930-03 (lanadelumab 300 mg every 4 weeks treatment arm) had low titre anti-drug antibodies positive samples at 3 visits; one positive low titre (40) sample obtained at an unscheduled visit was positive for neutralising antibodies and was of no apparent clinical consequence.

**Comment:** the safety results for the adolescent lanadelumab treated patients are consistent with that of the overall population and lanadelumab appeared to be well tolerated. However, the number of adolescent patients is small and the duration of treatment relatively brief given that lanadelumab is proposed for long term use. Of note is that only 8 adolescent patients have received lanadelumab treatment for 12 months or longer (with this including a dose-and-wait period that could last for several months and during which no lanadelumab was received).

### Post marketing data

Not applicable.

### Evaluator's conclusions on safety

Clinical experience with lanadelumab is limited and conclusions concerning safety must therefore be tentative. However, it appears to be well tolerated in clinical use at the dosing regimens that were found to have efficacy (150 mg every 4 weeks, 300 mg every 4 weeks and 300 mg every 2 weeks) and with no apparent evidence of dose related toxicity.

The clinical exposure of lanadelumab is limited to 257 unique individuals, with these comprising 24 healthy subjects who received a single dose of lanadelumab and 233

patients with HAE Type I or II who have received a variety of dosing regimens for periods of time that were, in general, brief. There have been only 57 patients who have received treatment for 12 months or more.

There were no deaths reported in any of the clinical studies involving lanadelumab. SAEs were infrequent and, in general, according to the narratives provided, unlikely to be due to lanadelumab. Treatment discontinuations due to adverse events were also rare, but did include AEs related to lanadelumab treatment, including hypersensitivity reactions and elevated transaminases.

In the double blind, placebo controlled Phase III Study DX-2930-03; AEs were reported in 76% of the patients in the placebo arm and 90% of the patients in the lanadelumab treatment arms. The AEs that were reported more frequently in lanadelumab treated patients were largely those due to injection site reactions (46% compared to 26%) with these including pain, erythema, bruising, discomfort, swelling, haematoma, haemorrhage. Similar high rates of injection site reactions were reported in the open label extension study DX-2930-04. Dizziness was reported more commonly in the lanadelumab treated patients in Study DX-2930-03 but was not consistently reported across the other studies. Headache was reported in similar proportions of lanadelumab treated and placebo patients.

The following conclusions regarding lanadelumab treatment can be tentatively drawn, although the evaluator recommends caution in the acceptance of these conclusions given the limited number of patients in the groups analysed:

- Evaluation of safety in patients in whom lanadelumab was recommenced after a treatment break of as long as 2 years identified no additional safety concerns, including no increased risk of the development of anti-drug antibodies or hypersensitivity reactions.
- An analysis of safety in a small number of patients receiving lanadelumab concurrent with other long term prophylaxis therapy (ies) whilst the latter were being weaned also identified no additional safety concerns.
- An analysis of AEs according to duration of therapy did not identify specific concerns although there appeared to be an increase in the proportion of patients in whom AEs were reported with increasing duration of treatment.
- Self-administration by trained patients/carers was evaluated in Study DX-2930-04 and was not found to result in an increase in injection site reactions. Other measures of safety with self-administration were not specifically reported.
- Testing for anti-drug antibodies in the clinical studies found low rates of positivity, with this commonly transient, of low titres, usually non-neutralising and not associated with any apparent differences in safety or efficacy.
- A separate presentation of safety in adolescents was provided. This indicated that safety in this group was similar to that of the overall population.

In terms of hypersensitivity reactions, there were no events of anaphylaxis or anaphylactoid reactions reported in any of the clinical studies. The hypersensitivity reactions that were reported were minor and included symptoms of tingling, itchiness, discomfort, headache and peripheral joint pain. In 2 patients, treatment was discontinued due to "hypersensitivity reaction". In one patient, this comprised peripheral joint pain and oedema that was treated with corticosteroids. In the other, the event consisted of a small area of maculopapular erythematous dermatitis that was itchy and close to the injection site and occurred with both the first and second dose of lanadelumab. These reactions were not related to the development of anti-drug antibodies.



Specific safety concerns related to lanadelumab include hepatotoxicity, rhabdomyolysis and bleeding risk:

- To date, hepatotoxicity appears to consist of mild elevation in transaminase levels with no reports of hepatic failure or Hy's Law cases. There were 10 patients in the two Phase III studies in whom significant ( $> 3 \times \text{ULN}$ ) but asymptomatic elevations of ALT and/or AST was reported. Four of these patients permanently discontinued treatment. Two patients had treatment withheld; in one this was recommenced without recurrence and the other had yet to recommence at the time of the interim report. Four patients continued lanadelumab with later normalisation of the transaminase levels in three and persistent elevation in one. Less significant elevations were reported to occur in  $< 5\%$  of patients.
- A number of patients have had elevated creatinine kinase levels reported during lanadelumab treatment, including one patient with the very high level of 22,000. Additional information has been requested of the sponsor regarding the possibility of myositis or rhabdomyolysis associated with lanadelumab treatment.
- Disordered coagulation is a theoretical concern with lanadelumab and clotting tests were monitored during the clinical studies. Mild increases, particularly in aPTT, were reported in a small number of patients. There did not appear to be an increased overall bleeding risk. However, the possibility of an increased local bleeding risk is suggested by the higher rate of injection site bleeding and bruising reported in lanadelumab treated patients compared to placebo patients in the Phase III study.

Overall, lanadelumab appears to be well-tolerated and to not be associated with serious adverse effects to date. However, it must be recognised that only small number of patients have been exposed and only for relatively short periods of time given that it is proposed for long term use.

## First round benefit-risk assessment

### First round assessment of benefits

**Table 16: First round benefits of lanadelumab by dose regimen**

| Effect   | Unit           | Lanadelumab       |                   |                   | Placebo | Strength of evidence | Comment   |
|--|----------------|-------------------|-------------------|-------------------|---------|----------------------|---|
|  |                | 150mg Q4W<br>N=28 | 300mg Q4W<br>N=29 | 300mg Q2W<br>N=27 | N=41    |                      |   |
| <b>Main or Pivotal Study DX-2930-03</b>                  |                |                   |                   |                   |         |                      |   |
| Median HAE attack rate in treatment period               | Attacks /month | 0.48              | 0.60              | 0.31              | 2.45    |                      |   |
| <b>Reduction in mean attack rate compared to placebo</b> | %              | 75.6              | 73.3              | 86.9              |         | P<0.001              | Consistent results all across secondary efficacy end-points and sub-group analyses. |
| Reduction in HAE attacks requiring treatment             | %              | 80.8              | 74.1              | 87.3              |         | P<0.001              |   |

The results of the placebo controlled Phase III study indicate a statistically significant and clinically important reduction in the incidence of acute HAE attacks in patients with HAE type I or II who receive prophylactic treatment with lanadelumab. The robustness of these results is indicated by consistency across the sensitivity analyses, secondary efficacy end-point results, the sub-group analyses and the results of the open label Phase III study and the Phase Ib study. The open label extension study found that the protective effect did not diminish over time.

The main caveats to these interpretations of favourable findings are the small size of the main efficacy study and the inherent intra- and inter-individual variability in HAE attack pattern and frequency. The effect of HAE attack pattern variability and the unpredictability of individual triggers is demonstrated by the three patients who were categorised as responders in Study DX-2930-03 but who subsequently became non-responders in Study DX-2930-04. The increase in HAE attack number during Study DX-2930-04 was attributed to 'significant life-changing stress events' experienced by each of the patients after rolling over into the open-label extension study. The effect of HAE attack pattern variability was also demonstrated by the substantial reduction in HAE attack rate per month in the placebo arm of Study DX-2930-03 (median 3.00 during the run-in period to median 1.69 attacks per month in the treatment period placebo arm). This inherent variability in HAE attack rates and the potential for unpredictable changes in life events to trigger attacks raises concerns regarding the results of the main efficacy study. Given the small number of patients included in the study, the results may be confounded by this variability and reflect changes in life events rather than the effects of lanadelumab.

### First round assessment of risks

**Table 17: First round risks of lanadelumab by dose regimen**

|                                  | DX-2930-03                   |                                  | DX-2930-04       |
|----------------------------------|------------------------------|----------------------------------|------------------|
|                                  | Placebo<br>(n = 41)<br>N (%) | Lanadelumab<br>(n = 84)<br>N (%) | n = 212<br>N (%) |
| Any AE                           | 31 (75.6)                    | 76 (90.5)                        | 182 (85.8)       |
| Any related AE                   | 14 (34.1)                    | 50 (59.5)                        | 89 (42.0)        |
| Any serious AE                   | 0                            | 4 (4.8)                          | 8 (3.8)          |
| Any severe AE                    | 4 (9.8)                      | 8 (9.5)                          | 21 (9.9)         |
| Discontinuation due to AE        | 1 (2.4)                      | 1 (1.2)                          | 5 (2.4)          |
| Hospitalisation due to AE        | 0                            | 4 (4.8)                          | 8 (3.8)          |
| Death due to AE                  | 0                            | 0                                | 0                |
| Transaminase elevation > 3 x ULN | 0                            | 4                                | 6                |
| creatinine kinase elevation      | 0                            | 0                                | 6                |
| Hypersensitivity reaction        | 0                            | 1                                | 6                |

|                            | DX-2930-03                   |                                  | DX-2930-04       |
|----------------------------|------------------------------|----------------------------------|------------------|
|                            | Placebo<br>(n = 41)<br>N (%) | Lanadelumab<br>(n = 84)<br>N (%) | n = 212<br>N (%) |
| aPPT elevation > 1.5 x ULN | 0                            | 1                                | 4                |

Lanadelumab was well tolerated in the patients included in the clinical studies. The main caveat to a favourable assessment of safety is the small number of exposed patients and the limited duration of therapy. It is likely that the full spectrum of less common adverse effects has yet to be identified and that such adverse events may substantially change the safety profile.

### First round assessment of benefit-risk balance

The use of long term prophylactic treatment is an accepted practice in some patients with HAE, although the precise criteria for determining when this should be commenced are unclear. In clinical practice, it is likely to be determined on an individual patient basis, according to the risk and impact of the disease on daily life.

The current long term prophylactic treatment options for HAE are limited. The preferred class of drugs for this in international guidelines are the C1-INH concentrates, with attenuated androgens recommended second-line. Due to funding arrangements in Australia, danazol is recommended first-line and C1-INH is available second-line. C1-INH requires twice weekly intravenous administration (although this may be performed by the patient/carer) and has been associated with rare but serious adverse events. The oral agent, danazol, has many side effects, requires monitoring during use, is contra-indicated in children and pregnancy but appears to be well accepted by patients and their treating doctors. The sponsor has provided a comparison of lanadelumab and C1-INH (IV and SC formulations) and androgens in the benefits and risks conclusions in the Clinical Overview. Much of this discussion appears to be centred around the other agents not eliminating the risk of acute attack. It is important to remember that lanadelumab also did not eliminate this risk.

Lanadelumab does offer the convenience of less frequent subcutaneous injections compared to C1-INH and clinical use to date suggests that it is both safe and efficacious. However, the small numbers investigated mean that any conclusions regarding safety and efficacy can only be tentative. The evaluator acknowledges that HAE is a rare condition and that this inevitably impacts on the clinical development programme for new pharmaceutical treatments. Pivotal studies for other new treatments in HAE that have been approved by regulatory bodies have also included small numbers as shown below.

**Table 18: Clinical study populations of TGA approved related products**

| Treatment                   | Pivotal study characteristics (as presented in the TGA approved PI) |
|-----------------------------|---|
| Acute attacks <sup>28</sup> |   |
| Cinryze                     | Phase III placebo controlled study of 71 HAE patients               |

<sup>28</sup> Clarification lanadelumab is not a comparator product for acute attacks

| Treatment                       | Pivotal study characteristics (as presented in the TGA approved PI)  |
|---------------------------------|--|
| Berinert                        | Phase III placebo-controlled, dose finding study of 124 HAE patients   |
| Icatibant                       | two phase III studies, one placebo controlled and one with tranexamic acid as comparator, with both together including a total of 130 HAE patients |
| Long term prophylaxis treatment |  |
| Cinryze                         | Phase III placebo controlled, crossover study of 22 HAE patients   |
| Haegarda                        | FDA approval based on a Phase III placebo controlled crossover study of 90 HAE patients  |

As with these other HAE treatments, the small evidence base would not preclude approval of lanadelumab due to the rarity of the condition and the potentially life-threatening effect of laryngeal attacks. However, it may be appropriate to limit prophylactic use to the patients most likely to benefit, that is, severely affected patients, who are intolerant to or insufficiently protected by oral prevention treatments or patients who are inadequately managed with repeated acute treatment. To ensure most appropriate use, treatment should be managed by a physician experienced in the care of patients with HAE, with regular review of the individual patients' benefit-risk balance.

#### ***Additional considerations that affect the benefit-risk assessment***

##### *Optimal dosing regimen*

Neither the optimal dose nor the optimal dosing frequency has been determined in the studies presented. The pivotal study investigated three treatment regimens (lanadelumab 150 mg every 4 weeks, 300 mg every 4 weeks and 300 mg every 2 weeks) but was not powered or designed to compare the treatment effect between the lanadelumab treatment arms. The open label extension study included one treatment regimen, lanadelumab 300 mg every 2 weeks. The sponsor has proposed that the regimen of 300 mg every 2 weeks be the recommended dose in the PI. The evaluator does not consider that this is supported by the evidence and recommends that the regimens investigated in Study DX-2930-03 be described as similarly efficacious. Appropriate individualising of treatment in the Australian context may be ensured by limiting initiation of treatment to suitably experienced physicians. The evaluator notes that this would be in keeping with the recommendation in the ASCIA position statement that patients are provided with an individual care plan by the treating specialist and that this 'may be accompanied by a letter from the specialist so it may be given to any treating physician unfamiliar with the individual and the condition.'

[Information redacted]

##### *Weight-based dosing*

Weight was found to be a major contributor to variability in lanadelumab pharmacokinetic and exposure is predicted to be higher in smaller patients, for example, 37% higher in adolescents compared to adults. Pharmacokinetic/pharmacodynamic analyses found that, in both small and large patients for each of the three regimens investigated in Study DX-2930-03, the concentrations achieved are in excess of the IC<sub>50</sub> for cleaved HMWK and monthly HAE attacks, and that inhibition of pKal is saturable at concentrations above the IC<sub>50</sub>. An analysis of efficacy end-points according to weight bands (40 to 79.9 kg, n = 44 and 80 to 150 kg, n = 40) with pooling of the lanadelumab treatment regimens for Study DX-2930-03 found similar results for the two weight bands. The sponsor has

concluded that there is no clinical benefit from weight-based dosing and argues that a single fixed dose simplifies administration.

The evaluator is of the opinion that the presented analyses indicate that the lower dose of 150 mg would be adequate in lower body weight patients. In the absence of definitive data, dosage advice should be broadly framed for example, in lower body weight patients.

### ***Benefit-risk assessment in adolescents***

The proposed indication is for a target population aged 12 years or older. The dossier does not include any dedicated studies performed in adolescents. Clinical experience in this population is limited to 10 patients aged 12 to 17 years in the main efficacy study and an additional 13 patients in the open label extension study. The evaluator does not consider that this is an adequate evidence basis for establishing safety and efficacy in this group. No weight adjusted dosing is proposed for adolescents, although the population pharmacokinetic analyses indicate that this will result in 37% higher exposure compared to adults.

The sponsor has argued that extrapolation of adult efficacy data to adolescents < 18 years for prevention of HAE is considered reasonable given existing evidence demonstrating similarities in disease. The evaluator recognises that obtaining robust evidence for efficacy in adolescents is limited by the rarity of the condition; that the disease is similar in adults and adolescents with onset of HAE most commonly during adolescence; that life-threatening events of laryngeal oedema have been reported in adolescence; and that there is an unmet need for long term prophylaxis in this population due to androgens being contra-indicated and twice weekly intravenous access potentially difficult. The evaluator also notes that generalisation of adult results to adolescents has been accepted by the TGA for the C1-INH concentrates in HAE treatments:

- The indication for Berinert does not specify patient age and the PI states that safety and efficacy of Berinert was not systematically evaluated in children.
- The indication for Cinryze includes adults and adolescents with this supported by an analysis of a subgroup of 46 children aged 2 to 17 years across 4 studies.

As the AusPAR for Cinryze notes;<sup>29</sup> 'The number of paediatric subjects evaluated in all these studies was too small to allow robust conclusion regarding efficacy and safety in this population'. The benefit-risk balance in this group appears to have been weighted towards favourable by limiting routine prophylaxis to more severely affected patients with frequent attacks of hereditary angioedema (HAE), who are intolerant to or insufficiently protected by oral therapy.

The evaluator recommends that, if lanadelumab is approved, a similar approach be taken with lanadelumab, with acceptance of generalisation of results from adults to adolescents provided the limitations to available evidence in adolescents is explicit in the PI. In view of the small dataset on which to assess safety, the evaluator also recommends that the dose of 150 mg should be considered in adolescents.

The evaluator notes that a Phase III, open label study to evaluate the safety, pharmacokinetics and efficacy of DX-2930 for prevention against acute attacks of HAE in children aged 2 to 11 years of age with type I and type II HAE is described in the RMP. According to the RMP, this study has been deferred to December 2018.

### ***Benefit-risk assessment in other sub-groups***

There are a number of sub-groups in whom an evidence-based benefit-risk assessment cannot be made due to the small numbers from these sub-groups included in the clinical

<sup>29</sup> AusPAR Cinryze C1 esterase inhibitor; Therapeutic Goods Administration, Canberra, Australia. 16 October 2013. <https://www.tga.gov.au/auspar/auspar-c1-esterase-inhibitor>

study programme. This includes patients with age > 65 years, patients with HAE type II, patients with significant hepatic or renal failure, patients of race other than white, patients with weight < 50 kg. This would not preclude approval of the use of lanadelumab in these sub-groups but it is important that the limitations of current data are explicit in the PI so as to enable prescribers and patients to make an individual benefit-risk assessment. There is no experience in children aged < 12 years, breast-feeding or lactating women, patients with significant hepatic impairment, patients with severe renal impairment.

#### *Generalisability to the Australian context*

The population treated in the main study may not be generalisable to the target population in Australia. Frequency of HAE attack may be a measure of disease severity. On this measure, the study population in the main efficacy study is likely to have much milder disease than the Australian population in whom parenteral long term prophylaxis may be considered as the inclusion criterion for the study was a minimum of one HAE attack per month whereas there is a requirement for 8 HAE attacks per month for funded access to C1-INH long term prophylaxis. The sponsor has been asked to comment on this see below.

#### *Lack of long term data and small numbers overall*

The small number of patients overall (n = 257) who have been exposed to lanadelumab and the very small number who have cumulative treatment of 12 months or more (n = 57) in the open label extension study to date create considerable uncertainty regarding the efficacy and safety as demonstrated to date. Given this uncertainty, it is essential that the limited knowledge base is explicit in the PI, that any approved use is limited to a group in whom the risk-benefit balance is most favourable (that is, patients with most severe disease) and that there are robust post-marketing pharmacovigilance measures. The latter may be best achieved by a patient registry as has occurred with some recently approved novel treatments for HAE.

## **First round recommendation regarding authorisation**

The evaluator is concerned by the considerable uncertainty resulting from the small number of patients treated in the pivotal study and by the potential lack of generalisability of the results of this study to the Australian target population. The evaluator has also asked a number of questions related to safety and made detailed recommendations regarding the PI. The sponsor's responses to these questions and recommendations must be evaluated and considered prior to the evaluator making any recommendation regarding authorisation.

## **Clinical questions and second round evaluation**

### **Background**

#### **Question 1**

***Nature of treatment and type of HAE in the proposed indication:*** The dossier presents the evidence for the use of lanadelumab as long-term prophylaxis in patients with HAE type I or II. The proposed wording with the phrase 'control of symptoms' could be interpreted as meaning that lanadelumab is also indicated in the treatment of acute attacks. The sponsor is asked to:

1. *justify the inclusion of the phrase 'control of symptoms' given the potential for misinterpretation and inappropriate use of lanadelumab; and*
2. *justify why the proposed indication does not limit the target population to the population investigated, that is, patients with HAE Type I and II*

*Summary of sponsor's response*

1. The sponsor agreed to remove the proposed wording with the phrase 'control of symptoms' from the indication for lanadelumab.
2. With respect to HAE, the sponsor acknowledged that three types have been identified and notes that the pathophysiology of HAE with normal C1-INH ('formerly known as type III') is yet to be understood. The sponsor provided some speculations regarding this pathophysiology and argues that the plasma kallikrein-kinin system, with unregulated pKal and excess bradykinin is also key to this. On this basis, the sponsor argues that the '*prevention treatment effects of lanadelumab could be extrapolated to HAE with normal C1-INH*'.

*Evaluator comment*

1. The sponsor's response is acceptable and information from the response has been incorporated into the body of the report in the relevant sections.
2. The evaluator does not agree that the '*prevention treatment effects of lanadelumab could be extrapolated to HAE with normal C1-INH*'. The evaluator notes that HAE with normal C1-INH (type III) is treated as a separate disease in clinical guidelines and that this approach has also been taken by the local funding body:
  - a. The ASCIA HAE position statement notes that HAE with normal C1-INH (type III) is a very rare condition and that '*this subtype will not be discussed in this document*'.
  - b. The 2017 International WAO/EAACI updated guideline for the management of HAE was limited to '*HAE with deficient C1-inhibitor (type 1) and HAE with dysfunctional C1-inhibitor (type 2)*' and states that '*Although HAE nC1-INH (HAE with normal C1-INH) shares some clinical features and, possibly, therapeutic options with HAE [types] I/II, this guideline is for HAE [types] 1/2*'.
  - c. The Australian NBA funds Berinert for long term prophylaxis in patients with HAE type I or II only.

The TGA has, in general, limited the target population to that investigated in the pivotal studies for the newer HAE treatments, as documented in the PIs. The exception to this is the wording of the indication for Berinert:

- The PI for Berinert states that '*Berinert is indicated for the treatment of acute attacks in patients with hereditary angioedema (HAE)*'. According to the AusPAR, the pivotal study included patients with abnormalities of C1-INH function.
- The PI for Cinryze specifies '*adults and adolescents with C1 inhibitor deficiency*'. The relevant study included only patients with Type I or II HAE.
- The PI for icatibant specifies that it is indicated in '*adults (with C1-esterase-inhibitor deficiency)*'.

Given the uncertainty around the pathophysiology of HAE with normal C1-INH (type III), the lack of information regarding efficacy of current HAE treatments due to the exclusion of this group from pivotal Phase III studies of new treatments, and the specific limiting of current guidelines to HAE types I and II, the evaluator recommends that the wording of the indication refers to the HAE types investigated in the clinical development programme of lanadelumab.



## Pharmacology

### Question 1

**Reversibility of the binding of lanadelumab to pKal:** *Reversibility of the effect of lanadelumab on cleaved HMWK levels was indicated by the return to pre-dose cleaved HMWK level by Day 120 in Study DX-2930-02. This was said to indicate that the binding of lanadelumab to pKal was reversible, although it may also occur through the production of new pKal. The sponsor is asked for more information regarding the nature of the binding of lanadelumab to the active binding site of pKal and what other evidence there may be to indicate that this binding is reversible.*

#### *Sponsor's response*

The sponsor presented the following information from non-clinical studies to support the reversibility of the binding of lanadelumab to pKal:

- the structure of the lanadelumab-pKal complex according to x-ray crystallography.<sup>30</sup> This found that the Fab section of lanadelumab extended into and completely obstructed the active site of pKal. Binding of lanadelumab to pKal involved hydrogen bonds, hydrophobic interactions and intra-molecular interactions. Alignment of lanadelumab in the protease active site of pKal is such that proteolysis of lanadelumab does not occur. Of note is that no covalent bonds were evident and that the active site of pKal is occluded by lanadelumab to an extent that even small peptides would be excluded from the pKal active site.
- enzyme kinetic analyses of the inhibition mechanism were reported to indicate reversible binding

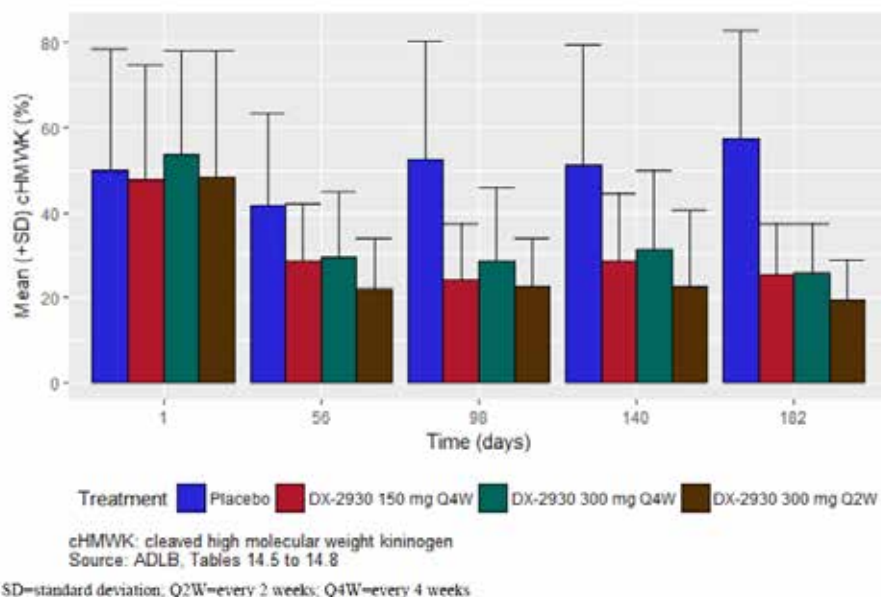
The sponsor noted that the pharmacodynamic investigations in Study DX-2930-02 were not performed at steady state and that the return to baseline activity of pKal could result from reversible binding with dissociation of the lanadelumab:pKal complex and/or generation of new pKal.

The sponsor postulated that, under steady state conditions with chronic administration of lanadelumab, the pKal level would remain stable due to a balance being reached between dissociation of lanadelumab-pKal complexes, new pKal formation, and new lanadelumab-pKal complex formation with new drug. To support this theory, the sponsor presented plots of cleaved HMWK level against time for the three dosing regimens in Study DX-2930-03 (see Figure 3).

The sponsor noted that new pKal may be produced during an HAE attack and speculated that the lanadelumab plasma concentration achieved with the dose of 300 mg every 2 weeks should be sufficient to bind the levels of pKal that have been reported during acute HAE attacks, thereby reducing the potential for new attacks.



**Figure 3: Study DX-2930-03: Mean (+ standard deviation) levels of cHMWK versus time, by treatment**



#### Evaluator comment

The evaluator accepts that the binding of lanadelumab to pKal is reversible. The evaluator also notes that breakthrough attacks were reported with all dosing regimens of lanadelumab as used in the Phase III studies. As noted by Kenniston et al.,<sup>30</sup> 'Pathophysiologic in vivo triggers of contact system activation in human disease have been difficult to identify' and the mechanism by which an acute HAE attack trigger then results in the generation of new pKal is not understood.

The pharmacokinetic/pharmacodynamic studies presented by the sponsor in the original dossier and the response to an earlier clinical question indicate that the inhibition of pKal by lanadelumab is a saturable process, with no appreciable increase in inhibition with lanadelumab concentrations above the IC<sub>50</sub> (cleaved HMWK formation rate was maximally reduced by 53.74% with an IC<sub>50</sub> of 5705 ng/mL). The steady state plasma concentrations (mean C<sub>ave,ss</sub>) for each of the dosing regimens investigated in Study DX-2930-03 were well above the IC<sub>50</sub> suggesting that each dosing regimen would be able to bind additional pKal.

#### Question 2

**Interaction with the pKal inhibitor ecallantide:** Both ecallantide and lanadelumab are reported to bind to the active binding site of lanadelumab. This raises the theoretical concern that the two agents will compete for the same site when co-administered and that this may decrease the effectiveness of ecallantide in the treatment of acute attacks. The sponsor is asked to provide an analysis of the patients who received ecallantide for acute attacks during treatment with lanadelumab and if there was any evidence to suggest that the effectiveness of ecallantide was decreased.

#### Sponsor's response

The sponsor reported that ecallantide is a 60 amino acid peptide engineered to selectively bind the active site of plasma kallikrein with high affinity and that x-ray crystallography studies have shown that lanadelumab blocks this active site. The mechanisms of action of acute attack treatments was described as either blocking bradykinin B2 receptor

<sup>30</sup> Kenniston, J. A. et al. 2014. Inhibition of plasma kallikrein by a highly specific active site blocking antibody. *JBiol Chem*, 289, 23596-608.

(icatibant) or by suppressing plasma kallikrein activity (C1-inhibitor, ecallantide). The sponsor postulated that acute attacks during lanadelumab treatment may occur '*due to the generation of plasma kallikrein levels at the attack location that exceed the molar amounts of lanadelumab in the circulation.*' The sponsor speculated that concomitant treatment with another inhibitor of plasma kallikrein (that is, ecallantide) in patients receiving lanadelumab should further decrease plasma kallikrein activity.

The effect of lanadelumab on ecallantide efficacy was investigated by comparing mean HAE attack duration in hours in the run-in period to the treatment period in those subjects who received ecallantide as a rescue therapy in Study DX-2930-03. Since the total number of subjects with ecallantide-treated attacks per treatment group was small (between 0 and 6 subjects), lanadelumab-treated subjects across dose groups were combined. This analysis found that there was no increase in attack duration where ecallantide was used before or during lanadelumab treatment (see Table 19).

**Table 19: Comparison of acute HAE attack duration during run-in and lanadelumab treatment periods**

| Run-in Period (4 to 8 weeks)  | Placebo<br>N=41   | Lanadelumab<br>N=84 |
|---|-------------------|---------------------|
| All attacks   |                   |                     |
| n (number of subjects)  | 41                | 84                  |
| n (number of attacks)   | 127               | 236                 |
| mean (SD) duration of attacks   | 28 (30.15)        | 31.7 (29.79)        |
| median (min, max) duration of attacks   | 18.0 (0.7, 179.0) | 22.8 (1.0, 157.0)   |
| All rescue medication treated attacks   |                   |                     |
| n (number of subjects)  | 37                | 75                  |
| n (number of attacks)   | 111               | 197                 |
| mean (SD) duration of attacks   | 25.6 (29.69)      | 29.4 (29.18)        |
| median (min, max) duration of attacks   | 16.0 (0.7, 179.0) | 18.8 (1.0, 157.0)   |
| Ecallantide-treated attacks   |                   |                     |
| n (number of subjects)  | 2                 | 10                  |
| n (number of attacks)   | 2                 | 16                  |
| mean (SD) duration of attacks   | 15.0 (13.86)      | 41.2 (36.24)        |
| median (min, max) duration of attacks   | 15.0 (5.2, 24.8)  | 30.8 (2.0, 119.5)   |
| Treatment Period (26 weeks)   |                   |                     |
| All attacks   |                   |                     |
| n (number of subjects)  | 40                | 52                  |
| n (number of attacks)   | 572               | 235                 |
| mean (SD) duration of attacks   | 32.3 (41.42)      | 28.6 (33.41)        |
| median (min, max) duration of attacks   | 20.5 (0.3, 559.0) | 19.5 (0.5, 292.0)   |
| All rescue medication treated attacks   |                   |                     |
| n (number of subjects)  | 40                | 42                  |
| n (number of attacks)   | 506               | 180                 |
| mean (SD) duration of attacks   | 29.7 (41.17)      | 25.9 (34.07)        |
| median (min, max) duration of attacks   | 18.0 (0.7, 559.0) | 16.0 (0.5, 292.0)   |
| Ecallantide-treated attacks   |                   |                     |
| n (number of subjects)  | 5                 | 7                   |
| n (number of attacks)   | 12                | 19                  |
| mean (SD) duration of attacks   | 12.0 (18.48)      | 36.6 (34.20)        |
| median (min, max) duration of attacks   | 4.2 (2.0, 65.9)   | 27.0 (5.2, 144.0)   |
| HAE=hereditary angioedema; ITT=intent-to-treat; SD=standard deviation; max=maximum; min=minimum                                 |                   |                     |
| Note: rescue medications include icatibant, C1 esterase inhibitor (C1-INH), ecallantide, Conestat alfa, and fresh frozen plasma |                   |                     |

A pharmacokinetic/pharmacodynamic analysis of the impact on cleaved HMWK levels according to whether ecallantide was or was not used for  $\geq 20\%$  of the treatment duration was presented. There were 7 patients who were reported to have had concomitant use for  $\geq 20\%$  of the treatment duration and 77 who did not. On the basis of this analysis, the sponsor concluded that the effect of ecallantide was additive.

The sponsor also referred to an analysis presented in the original dossier that purported to show that concomitant administration of ecallantide did not have any effect on lanadelumab CL/F or Vc/F.

#### Evaluator comment

The post hoc analysis of attack duration when treated by ecallantide before and during treatment with lanadelumab is reassuring and suggest that, on this measure, the efficacy of ecallantide is not altered by co-administration with lanadelumab. However, other

measures of acute attacks were not investigated (for example, time to onset of improvement, severity) and the table of results show extremely wide variation in attack durations. This, together with the small numbers in each group, limit the conclusions that may be drawn.

The evaluator notes that the use of ecallantide in Australia is likely to be very rare as, although it received Orphan Drug designation for use in HAE in 2011, it has not been approved by the TGA and is not included in the ARTG. The evaluator notes that ecallantide is only approved by the FDA and that an application to the EMA in 2011 was withdrawn. Despite this, it would be reasonable for a description of this theoretical pharmacodynamic interaction to be included in the PI with:

*An analysis of concomitant use of the ecallantide (a polypeptide that inhibits pKal by binding to the active site) for the treatment of acute HAE attack in lanadelumab treated patients found that the acute attack duration was not altered.*

### Question 3

**Patients with elevated AST and/or ALT in Study DX-2930-02:** According to the Review of lanadelumab (DX-2930) hepatic events in Phase III hereditary angioedema (HAE) prevention studies, in Study DX-2930-02, 'There were 6 subjects with ALT > 1 to < 3 x ULN during the treatment period in the 100 mg (n = 1), 300 mg (n = 1), 400mg (n = 1) and placebo (n = 3). One additional placebo subject had an elevated ALT > 3 x ULN.' These events are not discussed in the CSR or Summary of Clinical Safety as these discussions were limited to laboratory abnormalities that were reported as AEs. The sponsor is asked to provide more information regarding these subjects.

#### Sponsor's response

The sponsor identified 8 subjects in Study DX-2930-02 with elevated transaminases and provided the following information:

- all 8 subjects were asymptomatic, ALT elevations were transient and returned to baseline or near baseline without intervention
- 7 subjects had ALT elevations between > 1 to < 3 x ULN (upper limit of normal), and 1 subject had ALT elevations > 3 x ULN
- Of the 4 lanadelumab-treated subjects:
  - peak ALT elevation occurred prior to lanadelumab treatment in 2 subjects treated with lanadelumab 400 mg
  - peak ALT of 41 IU/L (1.24 x ULN) occurred during treatment in 1 subject treated with lanadelumab 100 mg
  - the same peak ALT of 42 U/L (1.02 x ULN) occurred both before and during treatment in one patient treated with lanadelumab 300 mg
- Of the 4 placebo patients
  - peak ALT elevation of 144 IU/L (4.36 x ULN) occurred prior to treatment in 1 subject
  - peak ALT elevation of 144 IU/L (4.36 x ULN) occurred during the treatment period in one patient who had an elevated ALT pre-treatment (67 IU/L)
  - peak ALT of 44 IU/L (1.07 x ULN) and 82 IU/L (2.48 x ULN) occurred during the treatment period in 2 patients respectively. Both had normal ALT levels pre-treatment.

The sponsor was of the opinion that there is no evidence that patients with HAE receiving lanadelumab are at increased risk of hepatotoxicity and did not agree with the proposed

inclusion of a special precaution regarding elevated transaminases due to hepatotoxicity or that hepatotoxicity should be considered an “important identified risk”. To support this the sponsor largely reiterated information provided in the dossier regarding the 10 of 233 (4.3%) subjects with HAE who have been exposed to lanadelumab in clinical trials and who experienced transaminase elevations  $> 3 \times \text{ULN}$ . The sponsor argued that this was not evidence of hepatotoxicity as:

- serious liver injury, as shown by cases of Hy’s law, acute liver failure, liver decompensation, serious adverse events due to transaminase elevations, as well as elevated bilirubin levels (with the exception of Gilbert’s disease), have not occurred.
- transaminase elevations were hepatocellular in nature and not dose (exposure)-dependent. Temporally, peak ALT elevations were variable and occurred anywhere from first to fourteenth active dose.
- Most of the patients had pre-existing transaminase elevation or suspected/documented liver diseases or exposure to other medication that could cause transaminase elevation:
  - 5 of 10 had elevated transaminases at Baseline
  - 6 of 10 had suspected or documented non-alcoholic fatty liver disease (NAFLD)
  - 3 of 10 had a history of prior androgen therapy based on available data (within 30 days prior to study).
- At longitudinal follow-up
  - 5 of 10 had resolution of transaminase elevations to baseline or near baseline [levels] without intervention, consistent with adaptation
  - 2 of 10 underwent rechallenge and both were negative (uneventful)
  - 2 of 10 discontinued due to asymptomatic elevation without sequelae
  - 1 of 10 had treatment ‘interrupted’ with a liver biopsy that was performed for persistent abnormalities showing cirrhosis. Evaluator comment: The response to a CHMP question reported that this patient did not subsequently recommence lanadelumab but commenced C1-INH for long term prophylaxis.

The sponsor also argued that data from the Study 03 revealed that there were the same percent in transaminase elevations, regardless of treatment with placebo or lanadelumab - each 4.8%.

The CHMP question asked, in part, for the sponsor to speculate regarding a ‘mechanistic rationale that lanadelumab would affect liver function’. The sponsor stated that when the liver is exposed to a new molecule liver adaptation and/or tolerance may occur, manifested by transient aminotransferase elevations. This is what was predominantly observed in these studies. The sponsor provided the following discussions but did not identify a mechanistic rationale for liver injury:

- Discussion of the liver’s involvement in the plasma kallikrein-kinin system with prekallikrein and cleaved HMWK produced in hepatocytes. The sponsor noted that as prekallikrein is not activated to kallikrein in hepatocytes, it could not be bound by lanadelumab. The sponsor recognised that the exact biochemical identities of endogenous triggers of kinin-kallikrein system activation have been challenging to elucidate and noted that the kinin-kallikrein system has been shown to be activated in various disease states.
- Discussion of the liver’s involvement in monoclonal antibody metabolism, noting that, as with immune complexes, the liver is expected to catabolise the complex formed when lanadelumab binds active plasma kallikrein with this mainly done by the Kupffer

cells and liver sinusoidal endothelial cells. Receptor-mediated endocytosis was reported to occur through binding to a site on the heavy chain of plasma kallikrein, whereas lanadelumab binds to the light chain.

*Evaluator comment*

Fully human mAbs are considered unlikely as a class to cause hepatotoxicity. However, a number of fully human mAbs (not including those used as antineoplastic agents) have been reported to be associated with hepatotoxicity, with the mechanism described as 'unknown' or 'probably immunologically mediated'. These mAbs include natalizumab, efalizumab, eculizumab, tocilizumab, and adalimumab. For most of these, hepatotoxicity became apparent after approval and manifested as asymptomatic elevations in transaminases, although there have also been rare reports of severe liver injury, including liver failure.

Hepatotoxicity with lanadelumab is also a concern to other regulatory bodies. The responses provided to the CHMP questions related to hepatotoxicity have been reviewed by the evaluator and were found to largely contain the same information and conclusions as those provided in responses to the TGA questions. Of note is that the only mention of transaminase elevation in the proposed PI and SmPC is their inclusion in the table of adverse reactions, with frequency reported as 'common'.

The FDA appears to have also been concerned by the effect of lanadelumab on the liver. This is shown by the inclusion of the following information in the Adverse Reactions section of the FDA approved label for lanadelumab:

Transaminase elevations

During the placebo controlled treatment period in Trial 1, the number of Takhzyro treated patients with maximum transaminase (ALT or AST) levels > 8, > 5, or > 3 times the upper limit of normal (ULN) was 1 (1.2%), 0 (0%), or 3 (3.6%) respectively, compared to 0 in the placebo treated patients. These transaminase elevations were asymptomatic and transient. No patients had elevated total bilirubin > 2 x ULN. One Takhzyro treated patient permanently discontinued treatment due to elevated transaminases (4.1 x ULN AST). None of the patients were reported to have serious adverse reactions of elevated transaminases.

The evaluator does not consider that the sponsor has adequately demonstrated that there is no safety concern regarding transaminase elevation and lanadelumab treatment. The 10 patients who experienced transaminase elevations > 3 x ULN in the clinical studies have been discussed in detail and no new information regarding these patients has been provided in the sponsor's responses. The evaluator does not agree that there were the same proportion of patients in Study DX-2930-03 with transaminase elevation in both the lanadelumab treatment arms and the placebo arm and notes that this is not supported by the data from the clinical study report. The evaluator does agree that the mechanism by which hepatotoxicity may occur is not evident but notes that the mechanism of liver injury with a number of other monoclonal antibodies has not been clearly identified. The evaluator also agrees that there have been no events to date of serious liver injury but, as with the CHMP, is concerned that there is the potential for more severe liver injuries in a larger treatment population.

The evaluator accepts that, given the imbalance of patients with metabolic syndrome in the lanadelumab treatment arms and that in one patient the transaminase elevation was likely from a skeletal muscle source, there is some uncertainty around the association between lanadelumab and hepatotoxicity. The evaluator therefore recommends that transaminase elevation be included in the RMP as an 'important potential risk' and that this information also be available in the PI. Given the uncertainty, the evaluator accepts that this would be most appropriately positioned in the Adverse Effects section of the PI

and, as has been done with the FDA approved label, proposes a subsection titled 'Laboratory Investigations' with wording such as that used in the FDA label.

#### Question 4

**Elevated creatinine phosphokinase and possible rhabdomyolysis in the clinical studies:** According to Study DX-2930-04, there were 6 participants in whom elevated creatinine phosphokinase was reported as AEs. These were graded as mild in 3 and moderate in 3. No other information regarding all of these events could be readily located by the evaluator. According to information presented regarding treatment interruption and hepatic events, there were two patients in whom high creatinine phosphokinase was reported in association with elevated AST and/or ALT, with the creatinine phosphokinase as high as 22,000 in one patient. This creatinine phosphokinase of 22,000 appears to have been attributed to strenuous activity. There were also two lanadelumab exposed subjects in Study DX-2930-01 in whom elevated creatinine phosphokinase was reported (and one placebo patient).

The evaluator is concerned that these AEs of elevated creatinine phosphokinase may represent a myositis or rhabdomyolysis secondary to lanadelumab.

The sponsor is asked to:

1. Provide more information regarding the 6 participants in Study DX-2930-04 in whom elevated creatinine phosphokinase was reported as AEs. This should include narratives if possible with detail provided regarding any strenuous exercise
2. Indicate if there have been any other lanadelumab exposed patients in the clinical development programme in whom elevated creatinine phosphokinase has been reported. Additional information, including clinical narratives, should be provided for any other patients so identified.
3. Indicate if any of the other patients in whom elevated AST and/or ALT was reported also had contemporaneous creatinine phosphokinase measurement and whether this was elevated.

#### Sponsor's response

The sponsor provided narratives for patients in whom creatinine kinase elevation had occurred in Study DX-2930-01 and Study DX-2930-04. The narratives included additional information from the clinical sites and updated safety data (as available). The information provided in the narratives has been summarised by the evaluator below.

**Table 20: Narrative summaries of patients in whom elevated creatinine kinase (creatinine kinase) was reported or recorded in Studies DX-2930-03, DX-2930-04 and DX-2930-01**

| Study      | Patient ID             | Demo-graphic<br>s | Lanadelumab<br>dose | Peak creatinine<br>kinase and Study<br>Day | Evaluator Comment                                     |
|------------|------------------------|-------------------|---------------------|--|---|
| DX-2930-03 | [information redacted] | F/44/W            | 150mg every 4 weeks | creatinine kinase 412 (ULN 192) Day 98     | No narrative provided. Baseline creatinine kinase 229 |

| Study                                     | Patient ID             | Demo-graphic<br>s | Lanadelumab<br>dose                           | Peak creatinine<br>kinase and Study<br>Day  | Evaluator Comment  |
|---|------------------------|-------------------|---|---|--|
| DX-2930-03 + DX-2930-04 Rollover patients | [information redacted] | M/54/W            | 150 mg every 4 weeks/<br>300 mg every 2 weeks | creatinine kinase 634 (ULN 37) approx. Day 56 of 03<br>creatinine kinase 974 (ULN 308) Day 15 of 04 | Attributed to 'regular deep tissue massages'; dates not provided in relation to creatinine kinase elevation                                    |
|   | [information redacted] | F/22/W            | 150 mg every 4 weeks/<br>300 mg every 2 weeks | creatinine kinase 1431 (ULN 192) approximately Day 112  | Attributed to 'stress and subsequent medications' following a sexual assault one month earlier. No other creatinine kinase elevation reported. |
|   | [information redacted] | F/29/W            | 300 mg every 2 weeks/<br>300 mg every 2 weeks | creatinine kinase 1333 (ULN 192) approx. Day 196  | Attributed to 'exercise/recreational play'. No further information   |
|   | [information redacted] | M/27/B            | Placebo/<br>300 mg every 2 weeks              | creatinine kinase 6399 (ULN 308) with AST/ALT elevation approx. Day 56                              | Attributed to 'intense heavy exercise training sessions to lose weight prior to the visit'. Smaller elevation Day 112 (creatinine kinase 395)  |
|   | [information redacted] | F/28/W            | 300 mg every 2 weeks/<br>300 mg every 2 weeks | creatinine kinase 3548 with AST/ALT elevation Day 196   | No cause found – no recent exercise, trauma et cetera.   |
|   | [information redacted] | F/38/W            | 300 mg every 4 weeks/<br>300 mg every 2 weeks | creatinine kinase 438 approx Day 112  | Attributed to hiking in hot weather 3 days prior.  |
|   | [information redacted] | F/44/W            | 150 mg every 4 weeks/<br>300 mg every 2 weeks | creatinine kinase 527 approx Day 168;<br>creatinine kinase 362 approx Day 196                       | Persistent mild elevation throughout including baseline – creatinine kinase 200 to 300. Attributed to 'regular athletic activities'.           |



| Study                            | Patient ID             | Demo-graphic s | Lanadelumab dose     | Peak creatinine kinase and Study Day  | Evaluator Comment  |
|----------------------------------|------------------------|----------------|----------------------|---|--|
| DX-2930-04 Non-Rollover patients | [information redacted] | M/57/W         | 300 mg every 2 weeks | creatinine kinase 2761 (ULN 308) Day 184  | Attributed to 'working out in the gym after 3 months of inactivity'  |
|                                  | [information redacted] | F/27/W         | 300 mg every 2 weeks | creatinine kinase 909 (ULN 192) Day 225 of 04   | Attributed to 'HAE attack in area of Trauma' 6 days before creatinine kinase elevation   |
|                                  | [information redacted] | M/37/W         | 300 mg every 2 weeks | creatinine kinase 2200 (ULN 308) with AST/ALT elevation<br>Day 155<br>3210 (ULN 308) with AST/ALT elevation<br>Day 227                | First episode: AEs of 'muscle tightness' and upper respiratory tract infection reported at the time. Treatment interrupted due to concurrent AST/ALT elevation. Cause of creatinine kinase elevation not clear; 'could be result of exercising with fever' but no description of exercise given.<br><br>No cause described with second episode; treatment discontinued |
|                                  | [information redacted] | M/47/W         | 300 mg every 2 weeks | creatinine kinase > 22000 (> 10 x ULN) with AST/ALT elevation Day 30<br>creatinine kinase 1693 approximately 120 days after last dose | Received 3 of 12 planned doses – interrupted due to AST/ALT (creatinine kinase) elevation and not recommenced. Creatinine kinase elevation attributed to 'history of strenuous exercise' and subject non-compliant with exercise restriction. Baseline creatinine kinase 300   |
|                                  | [information redacted] | F/55/W         | 300 mg every 2 weeks | creatinine kinase 1254 approximately Day 168;<br>creatinine kinase 380 approximately Day 42   | Major episode attributed to heavy lifting – patient described muscle soreness at the time.   |



| Study  | Patient ID             | Demo-graphic<br>s | Lanadelumab<br>dose | Peak creatinine<br>kinase and Study<br>Day         | Evaluator Comment   |
|--|------------------------|-------------------|---------------------|--|---|
| DX-2930-01   | [information redacted] | F/24/B            | 0.1 mg/kg           | creatinine kinase 902 (ULN 215) Day 21 after dose  | Smaller creatinine kinase elevation at Days 84 (creatinine kinase 272) and 112 (creatinine kinase 345)  |
|  | [information redacted] | F/29/W            | 3 mg/kg             | creatinine kinase 2179 (ULN 215) Day 42 after dose | Attributed to 'fitness instructor with strenuous activity levels' although no other creatinine kinase elevation during observation period.                                  |
|  | [information redacted] | M/23/B            | 0                   | creatinine kinase 1967 (ULN 294) Day 42 after dose | Smaller creatinine kinase elevations on Day 7 (creatinine kinase 299), Day 21 (creatinine kinase 299), Day 28 (creatinine kinase 304), and Day 112 (creatinine kinase 341). |
| # Creatinine phosphokinase elevations not reported as an AE; *Patient not included in sponsor's response |                        |                   |                     |  |   |

The sponsor provided a brief discussion of creatinine kinase elevation with exercise or heavy manual labour and that this may also be associated with AST/ALT elevation. The sponsor concluded that for the cases of creatinine kinase elevation in the lanadelumab programme: the majority occurred after exercise, massage, or laborious work; all subjects were asymptomatic and there were no clinical signs or symptoms suggestive of myositis or rhabdomyolysis; the Applicant has no concerns of myositis or rhabdomyolysis secondary to lanadelumab treatment.

#### *Evaluator comment*

The evaluator accepts that exercise may be associated with an elevation in creatinine kinase, together with AST and ALT, and that the clinical significance of exercise-induced elevation is unclear as the renal complications associated with classic rhabdomyolysis are not observed. However, it is also recognised that there are a number of drugs that are associated with myopathy/ myositis/rhabdomyolysis and it is speculated that such drugs may also increase the release of creatinine kinase during exercise. Drugs associated with myopathy and myositis include therapeutic mAbs such as the check-point inhibitors. The evaluator recognises that the cause of skeletal muscle involvement with check-point inhibitors is considered to be immune system mediated and that a biologically plausible mechanism by which lanadelumab may cause skeletal muscle injury is not clear. Against this is the imperfect understanding of the kinin-kallikrein system and its functions in health and disease and potential impurities in the lanadelumab drug product.

The sponsor provided narratives for a total of 15 subjects in whom creatinine kinase elevation was reported or recorded. Of these 14 of 15 subjects had received or were receiving lanadelumab. As evident in the table above, not all of the episodes of elevated creatinine kinase were associated with exercise or trauma. It is also not clear why some

subjects who had regular strenuous activity levels had only one spike in creatinine kinase during the period of observation. The subjects in whom marked creatinine kinase elevation occurred did not have any of the clinical features of rhabdomyolysis although some complained of muscle pain (described as 'tightness' or 'soreness').

The evaluator has examined the clinical study reports for more information. The number of patients at each time-point in whom an elevated creatinine kinase was recorded is shown in the tables below.

**Table 21: Study DX-2930-03 Results of 'High creatinine kinase' during study**

| Placebo n = 41                        |  |                        |          | All lanadelumab treatment n = 84           |                        |           |
|---------------------------------------|--|------------------------|----------|--|------------------------|-----------|
|                                       | Number (%) with elevated creatinine kinase |                        |          | Number (%) with elevated creatinine kinase |                        |           |
| Time Point*                           | Not clinically significant                 | Clinically significant | All      | Not clinically significant                 | Clinically significant | All       |
| Day 0                                 | 2 (4.9)                                    | 0                      | 2 (4.9)  | 3 (3.6)                                    | 0                      | 3 (3.6)   |
| Day 28                                | 1 (2.6)                                    | 0                      | 1 (2.6)  | 5 (6.4)                                    | 0                      | 5 (6.4)   |
| Day 56                                | 1 (2.7)                                    | 0                      | 1 (2.7)  | 6 (7.4)                                    | 0                      | 6 (7.4)   |
| Day 98                                | 1 (2.7)                                    | 0                      | 1 (2.7)  | 3 (3.8)                                    | 1 (1.3)                | 4 (4.8)   |
| Day 140                               | 1 (2.8)                                    | 0                      | 1 (2.8)  | 5 (6.3)                                    | 0                      | 5 (6.3)   |
| Day 182                               | 1 (2.6)                                    | 0                      | 1 (2.6)  | 2 (2.5)                                    | 0                      | 2 (2.5)   |
| Total                                 | 7 (17.1)                                   | 0                      | 7 (17.1) | 24 (28.6)                                  | 1 (1.3)                | 25 (29.8) |
| *Numbers at each timepoint could vary |  |                        |          |  |                        |           |

In patients receiving lanadelumab in Study DX-2930-03, musculoskeletal pain was reported as an AE in 3.6% of patients, myalgia in 4.8% and muscle tightness in 1.2%. These AEs were not reported in any of the patients from the placebo arm.

**Table 22: Study DX-2930-04 Results of 'High creatinine kinase' during study**

| Rollover<br>n = 109 |  |                        |         | Non-rollover<br>n = 103                    |                        |         | All<br>n = 212                             |
|---------------------|--|------------------------|---------|--|------------------------|---------|--|
|                     | Number (%) with elevated creatinine kinase |                        |         | Number (%) with elevated creatinine kinase |                        |         |  |
| Time Point*         | Not clinically significant                 | Clinically significant | All     | Not clinically significant                 | Clinically significant | All     | Number (%) with elevated creatinine kinase |
| Day 0               | 4 (3.7)                                    | 0                      | 4 (3.7) | 9 (8.7)                                    | 0                      | 9 (8.7) | 13 (6.1)                                   |

|  | Rollover<br>n = 109 |         | Non-rollover<br>n = 103 |         |         | All<br>n = 212 |          |
|--|---------------------|---------|-------------------------|---------|---------|----------------|----------|
| Day 28   | 5 (5.1)             | 1 (1.0) | 6 (5.5)                 | 7 (7.1) | 0       | 7 (7.1)        | 13 (6.1) |
| Day 56   | 6 (5.8)             | 0       | 6 (5.8)                 | 5 (5.0) | 1 (1.0) | 6 (6.0)        | 12 (5.9) |
| Day 98   | 3 (2.9)             | 1 (1.0) | 4 (3.9)                 | 7 (7.3) | 0       | 7 (7.3)        | 11 (5.5) |
| Day 154  | 8 (8.0)             | 0       | 8 (8.0)                 | 5 (5.2) | 1 (1.0) | 6 (6.2)        | 14 (7.1) |
| Day 182  | 6 (6.0)             | 1 (1.0) | 7 (7.0)                 | 4 (5.7) | 1 (1.4) | 5 (7.1)        | 13 (7.7) |
| Day 224  | 7 (10.0)            | 0       | 7 (10.0)                | 1 (2.9) | 1 (2.9) | 2 (5.7)        | 9 (8.6)  |
| *Numbers at each timepoint could vary. Only timepoints with 100 or more subjects in total included |                     |         |                         |         |         |                |          |

In Study DX-2930-04, musculoskeletal pain was reported as an AE in 2.4% of patients, myalgia in 1.4% and muscle tightness in 0.9%.

The results from Study DX-2930-03 allow comparison to the placebo arm and show a substantially higher incidence of “High creatinine kinase” in the lanadelumab treated group (around 6% compared to 3% at each time-point during the treatment period and 29.8% compared to 17% overall). Of note is that no patients from the placebo arm had AEs related to muscle pain reported, compared to 9.6% of lanadelumab treated patients. The results for “High creatinine kinase” from Study DX-2930-04 show that the average incidence was similar in the rollover and non-rollover patients across the time-points (around 6%) and similar to the lanadelumab treated subjects in Study DX-2930-03. AEs related to muscle pain were reported in a lower proportion (4.7%) of patients compared to the lanadelumab-treated patients in Study DX-2930-03.

The evaluator is of the opinion that there is a possible safety signal of elevated creatinine kinase during lanadelumab treatment, and that this may be associated with muscle symptoms of pain or tightness. The evaluator notes that there were two lanadelumab-treated subjects in whom treatment was discontinued due to creatinine kinase elevation. The evaluator speculates that there may be low-grade persistent elevation in many patients, with exaggerated release of creatinine kinase in response to exercise in some patients. The evaluator recognises that there have been no reports of rhabdomyolysis with lanadelumab use to date but notes that only 257 individuals have been exposed to lanadelumab. The evaluator recommends that creatinine kinase elevation during treatment be included as an “important potential risk” in the RMP and that information regarding this risk should be included in the Adverse Effects section of the PI:

Creatine kinase (creatinine kinase) elevation has been reported during lanadelumab treatment, with clinically important elevation following exercise in a small number of patients (> 5 times upper limit of normal in 6 patients and > 10 times upper limit of normal in 1 patient). These elevations were asymptomatic and transient. No episodes of rhabdomyolysis or serious adverse reactions of elevated creatinine kinase were reported. Treatment was discontinued in 2 patients due to creatinine kinase elevation together with transaminase elevation.

## Benefit-risk assessment

### Question 1

#### **Generalisability of the results of Study DX-2930-03 to the Australian target population:**

The current standard of care in Australia is that parenteral long term prophylaxis is considered only if very frequent attacks occur. This is demonstrated by the requirement for funded access to C1-INH that the patient must be experiencing 8 attacks per month despite oral agents. There were very few patients in Study DX-2930-03 who would have met these requirements: the median number of attacks in the last 3 months was 7, although the range was up to 90; the highest strata of run-in attack rate was  $\geq 3$ . The sponsor is asked:

- how many of the patients in Study DX-2930-03 had a baseline attack rate that was greater than 8 per month
- how many patients with a baseline attack rate of greater than 8 per month were receiving prior long term prophylaxis, and the type of long term prophylaxis
- if the results for the patients with a baseline attack rate of greater than 8 per month were consistent with the main group, accepting that this is a post-hoc analysis and may involve only a small number of patients.

#### *Sponsor's reply*

The sponsor stated that, in Study DX-2030-03, 7 of the 125 (5.6%) subjects had an HAE attack rate of  $> 8$  attacks/month during the run-in period and that all 7 of these patients were receiving long term prophylaxis with C1-INH prior to study entry. Of the 7 patients, 4 were randomised to the placebo arm and 3 were randomised to the active treatment arms (150 mg every 4 weeks  $n = 0$ ; 300 mg every 4 weeks  $n = 1$ ; 300 mg every 2 weeks  $n = 2$ ). The efficacy analysis reported by the sponsor found that for this sub-group of 7 patients with baseline attack frequency  $> 8$  per month, a lower mean (SD) HAE attack rate during the treatment period was observed in the 3 lanadelumab treated subjects (1.38 (1.32)) compared to the mean (SD) HAE attack rate in the 4 placebo treated subjects (5.76 (3.43)), and the results were consistent with the results observed in the well-represented main category (see also Table 23).

**Table 23: Percent relative reduction in HAE attack rate during treatment period (Day 0 to182) and Steady State Period (Day 70 to182) in Study DX-2930-03**

|   | Comparing Lanadelumab Treatment Groups            |   |
|---|---|---|
|   | 300 mg q2wks (N=27)<br>vs.<br>150 mg q4wks (N=28) | 300 mg q2wks (N=27)<br>vs.<br>300 mg q4wks (N=29) |
| Number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)<br>% Reduction in mean HAE attack rate relative to 150 mg q4wks or 300 mg q4wks (95% CI)                           | 46%<br>(-10, 74)                                  | 51%<br>(2, 75)                                    |
| Number of investigator-confirmed HAE attacks during the estimated steady state period, Day 70 through Day 182 <sup>a</sup><br>% Reduction in mean HAE attack rate relative to 150 mg q4wks or 300 mg q4wks (95% CI) | 62%<br>(5, 85)                                    | 56%<br>(-9, 82)                                   |
|   | 300 mg q2wks (N=27)<br>vs.<br>150 mg q4wks (N=28) | 300 mg q2wks (N=27)<br>vs.<br>300 mg q4wks (N=29) |

CI=confidence interval; HAE=hereditary angioedema  
a. Placebo N=37; lanadelumab 300 mg q2wks N=26

The sponsor noted that the sub-group had too small number of patients for inferential conclusion regarding the HAE attack rate in comparison to placebo to be drawn.

*Evaluator comment*

There are currently two accepted approaches to long term management of HAE: on-demand treatment alone or on-demand treatment plus long term prophylaxis. The use of long term prophylaxis has been described as controversial by some due to the effectiveness of newer acute attack treatments and there are no generally accepted criteria for the introduction of long term prophylaxis.

Treatment options in Australia are further limited by regulatory and funding status of newer agents. As described above, the ASCIA Health Professionals Position Paper on Hereditary Angioedema (2017) recommends first-line long term prophylaxis with oral androgens (danazol) and that C1-INH (Berinert) should be used second line in accordance the National Blood Authority approved indication (patients who experience the equivalent of eight or more acute attacks per month).

Given that the pivotal study included only 7 patients with baseline attack rate > 8 per month, there is insufficient data to determine if Australian patients with HAE who would be considered for parenteral long-term prophylaxis would benefit from the administration of lanadelumab. The sponsor has argued that this attack rate requirement is a reimbursement requirement and that lanadelumab will undergo a different funding pathway. This argument does not allow for the current uncertainties around the benefit, or otherwise, of long term prophylaxis in patients with milder disease. These uncertainties are demonstrated in the clinical guidelines that recommend long term prophylaxis only in severely symptomatic patients who fail to achieve adequate control with appropriate on-demand therapy. The evaluator does not consider that lanadelumab does not offer patients freedom from acute attacks and the need to carry on-demand treatments at all times.

Given the uncertainty regarding generalisability to the Australian population and the overall uncertainties due to the limited evidence basis for safety and efficacy, the evaluator recommends that the indication limit use to patients with severe disease with:

*Takhzyro is indicated for routine prevention of angioedema attacks in patients aged 12 years and older with hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) who have frequent severe attacks and who are inadequately controlled by on-demand treatments.*

## Dosing recommendations

### Question 1

**Dosing interval and drug holidays:** Pharmacodynamic investigations have shown persistent inhibition of plasma kallikrein for up to 120 days after two doses on lanadelumab two weeks apart. The dose-and-wait period in rollover patients in Study DX-2930-04 found a lasting effect in terms of HAE attack reduction of more than 10 weeks in around 30% of patients. This may indicate that a longer dosing interval than 2 or 4 weeks may be adequate or that “drug holidays” may be considered with long term use.

1. The sponsor is asked if any investigations of a longer dosing interval are planned.
2. The evaluator proposes that the PI include a statement that: “Treatment cessation may be considered after 6 months of continuous prophylactic treatment, with this to be recommenced with the first HAE attack after the regular dosing interval.” The sponsor is asked to comment.
3. To facilitate inclusion of information relevant to b) in the Clinical Trials section of the PI, the sponsor is asked to provide a presentation of the time to first HAE attack for Study



*DX-2930-04 rollover patients from the lanadelumab treatment arms in Study DX-2930-03. This should show the group as a whole (that is not broken down according to DX-2930-03 lanadelumab dosing regimen) and should not include patients from the placebo arm of Study DX-2930-03. The presentation should include the median time to first HAE attack (min, max). A histogram with number of patients against time intervals of 1 month would be also be helpful.*

#### *Sponsor's response*

The sponsor indicated that no investigation of a longer dosing interval is planned.

The sponsor did not accept the evaluator's recommendations regarding the equivalence of the three dosing regimens, consideration of a 'drug holiday' after 6 months of continuous treatment and weight-based dosing. Instead the sponsor proposed that 'the dosing regimen to be as follows (which is identical with the wording as recently approved by US FDA and as proposed to EMA)':

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 if the patient is well-controlled (for example, attack free) for more than 6 months.

In making this recommendation the sponsor stated that 'the sponsor believes 300 mg every 2 weeks should be the recommended dosing to prevent the risk of the breakthrough attacks. Nevertheless, the Applicant acknowledges that for some patients a dosing interval of every 4 weeks (300 mg every 4 weeks) may be considered if the patient is well controlled for 6 months on 300 mg every 2 weeks'.

*Starting dose:* To support the recommendation of the starting dose of 300 mg every 2 weeks, the sponsor largely reiterated the arguments that had been presented as a rolling response to an earlier clinical question.

*'Drug holiday' and request for further information regarding the median (min, max) time to first attack in the rollover patients in Study DX-2930-04:* The sponsor did not provide the requested information on the median time to first attack during the dose-and-wait period on the basis that the inclusion of this information in the PI may be 'misleading to healthcare providers' and 'may be misinterpreted as permissive guidance to stop dosing ('watch and wait') or stretching the dosing interval'. The sponsor expressed the concern that this could expose patients to "life-threatening angioedema attack". Instead of providing the requested observed data, the sponsor provided the analysis showing estimated percentage of patients with first HAE attack at different weeks as was provided in the Study DX-2930-04 (see Table 24).

**Table 24: Study DX-2930-04: Time to first HAE attack- rollover subjects**

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

The sponsor further argued that 'the 'dose and wait' period analysis and results are based on a heterogeneous population consisting of patients with different background levels of

disease activity and lanadelumab concentrations such that the clinical significance of the median number of days to first HAE attacks for all rollover subjects is challenging to understand and interpret'. The sponsor stated that the treatment strategy should be based on rigorous study data and the label should rather present factual study results than subjective recommendations.

Justification for the sponsor's proposed recommendation '*A dosing interval of 300 mg every 4 weeks is also effective and may be considered if the patient is well-controlled*'.

The sponsor noted that the primary goal of prophylactic therapy for HAE is to prevent angioedema attacks and provide patients with the best opportunity to live a normal life and that '*freedom from angioedema attacks for at least six months can provide an unambiguous guidance to health care providers regarding patients that may be considered for a less frequent dose regimen*'. The six month timeframe was reported to be based on the clinical practice and the efficacy data obtained from the pivotal Study DX-2930-03. The sponsor noted that this recommendation would allow for some flexible dosing and would "harmonize with the dosing regimen in other regions (for example, the United States)". The sponsor also noted that 'the sponsor also understands the need for clinicians to individualize therapy, including an opportunity for flexible dosing. Extending the dosing interval beyond every 2 weeks to every four weeks potentially represents a substantial quality of life benefit for patients'.

#### *Evaluator comment*

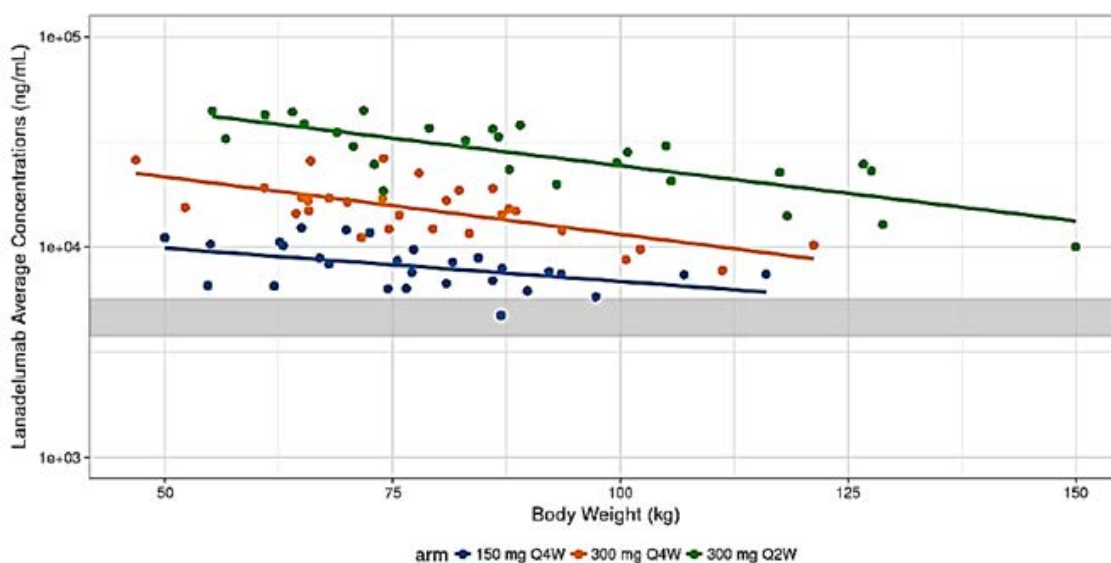
*Starting dose:* The sponsor has presented no new information to justify the proposed starting dose of 300 mg every 2 weeks. The evaluator remains of the opinion that the totality of evidence favours weight-based dosing and that there is no conclusive evidence to support the dosing regimen of every 2 weeks over every 4 weeks. The basis for this opinion has been presented in interim report and in the evaluation of the sponsor's responses to rolling questions. These may be summarised as:

- Exposure has been shown to increase with lower body weight, with an estimated increase in exposure of 37% in adolescents
- The inhibition of pK<sub>1</sub> by lanadelumab is a saturable process, with this plateauing at plasma lanadelumab concentrations above the IC<sub>50</sub>. Average steady state concentration for each of the three dosing regimens used in the pivotal study were above the IC<sub>50</sub>.
- The pivotal study did not show a significant difference in efficacy across the three dosing regimens investigated, and was not powered or designed to demonstrate any difference.

The evaluator recognises that it is preferable where possible to provide more specific dosing advice than that recommended below but does not consider that there is an adequate evidence basis for the dosing regimen proposed by the sponsor. The evaluator is of the opinion that a flexible dosing recommendation would not compromise the patient given that the dosing decisions will be made by physicians experienced in the care of HAE patients. Dealing with dosing flexibility would be well within the capability of such physicians as the care of HAE patients routinely involves the development of individual patient care and action plans that address preventive measures, home care and self-administration of on-demand and long term prophylaxis treatments.

*Weight based dosing:* As noted above, the issues around weight-based dosing were discussed through the rolling response process. In addition, the evaluator notes the concerns raised in the CHMP regarding the potential for under-dosing patients with higher body weight. This potential is also suggested by the display of the relationship between body weight, steady state average lanadelumab concentrations and the IC<sub>50</sub> for cleaved HMWK (see Figure 4).

**Figure 4: Relationship between body weight and lanadelumab average concentrations at steady state ( $C_{ave,ss}$ ) relative to  $IC_{50}$  for cleaved HMWK and monthly HAE attack rate)**



The evaluator is of the opinion that weight-based dosing offers benefits to the patient, with a starting dose of 150 mg in patients with body weight < 50 kg and starting dose of 300 mg for patients with body weight > 100 kg. The dose of 150 mg in patients with body weight < 50 kg would not compromise efficacy (noting that the results of the pivotal study) and would provide the patient-important benefit of only needing one injection per dose. The process of administering this dose would be simple as the sponsor has proposed that lanadelumab be provided in two vial sizes (150 mg in 1 mL and 300 mg in 2 mL). The dose of 300 mg in patients weighing more than 100 kg would reduce the potential for under-exposure and reduced efficacy in these patients.

The evaluator recognises that the FDA approved label includes the sponsor's proposed statement with this indicating that the opinion of that regulatory body is that weight-based dosing is not necessary. The opinion of the CHMP is not yet known.

*Drug holiday:*<sup>31</sup>

[Information redacted]

The evaluator also raised questions relating to the PI do and RMP but these do not form part of the AusPAR and have been redacted.

## Second round benefit-risk assessment

The assessment of benefits is largely unchanged from the Interim Report.

The assessment of risk is improved in that the information provided to date does not identify lanadelumab treatment as a cause of hepatotoxicity or rhabdomyolysis, although it appears to be associated with transaminase elevation and creatinine kinase elevation. It is unknown whether more severe manifestations of liver and skeletal muscle injury may be reported with wider use.

<sup>31</sup> For the final recommendations on dosage for long term prophylaxis please see the Product Information. The TGA has redacted this section as the final dosing recommendations of the Delegate and the ACM did not include the use of a 'drug holiday'



The evaluator is of the opinion that the benefit-risk is only positive for patients with severe disease and recommends that the wording of the indication should limit use to such patients with the following:

*Takhzyro is indicated for routine prevention of angioedema attacks in patients aged 12 years and older with hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) who have frequent severe attacks and who are inadequately controlled by on-demand treatments.*

This opinion is based on:

- the uncertainty regarding efficacy due to the small numbers investigated in the pivotal study and the inherent intra- and inter- variability in HAE attack rates
- the uncertainty regarding safety due to the small numbers of patients exposed to lanadelumab, particularly with long term use
- the uncertainty regarding generalisability to the Australian population
- the consensus in clinical guideline regarding a lack of benefit from long term prophylaxis in patients with mild HAE s

The evaluator's benefit risk assessment is also predicated on the sponsor accepting the evaluator's recommendations regarding dosing regimen and presentation of safety concerns in the PI, CMI and RMP. If these are not agreed to by the sponsor then the benefit-risk assessment would be altered.

The evaluator recommends that lanadelumab be approved for long term prophylaxis in patients with HAE but that this should be limited to patients with severe disease. The evaluator recommends the following wording:

*Takhzyro is indicated for routine prevention of angioedema attacks in patients aged 12 years and older with hereditary angioedema (C1-esterase-inhibitor deficiency or dysfunction) who have frequent severe attacks and who are inadequately controlled by on-demand treatments.*

In making this recommendation for approval, the evaluator has assumed that the recommendations made regarding the product documentation will be accepted by the sponsor, with this including the recommendations for weight-based dosing.

## VI. Pharmacovigilance findings

### Risk management plan

The sponsor has submitted EU-RMP version 1.1 (26 July 2018; data lock point 1 September 2017) and Australian-specific Annex (ASA) version 1.0 (dated 26 July 2018) in support of this application. The sponsor submitted an updated EU-RMP version 1.5 dated 16 October 2018, data lock point 1 September 2017 with ASA version 1.2 dated 10 January 2019. The updated EU-RMP has included 'use in pregnancy and lactation' as missing information.

**Table 25: Sponsor's Summary of safety concerns**

| Summary of safety concerns |                  | Pharmacovigilance |            | Risk Minimisation |            |
|----------------------------|------------------|-------------------|------------|-------------------|------------|
|                            |                  | Routine           | Additional | Routine           | Additional |
| <b>Important</b>           | Hypersensitivity | Ü                 | Ü*         | Ü+                | –          |

| Summary of safety concerns       |   | Pharmacovigilance |    | Risk Minimisation |   |
|----------------------------------|---|-------------------|----|-------------------|---|
| <b>identified risks</b>          |   |                   |    |                   |   |
| <b>Important potential risks</b> | Immunogenicity                            | Ü                 | Ü* | Ü+                | – |
|                                  | Liver toxicity                            | Ü                 | Ü* | Ü                 | – |
| <b>Missing information</b>       | Long-term safety in paediatric population | Ü                 | Ü* | Ü+                | – |
|                                  | Long-term safety in adult population      | Ü                 | Ü* | Ü+                | – |
|                                  | Use in pregnancy and lactation ‡          | Ü                 | –  | Ü+                | – |

\* Clinical study: HELP Study Extension DX-2930-04; + CMI package insert; ‡ Included in EU-RMP version 1.5

### Summary of RMP evaluation<sup>32</sup>

The safety concern ‘use in pregnancy and lactation’ was added in the updated EU-RMP version 1.5.

The additional pharmacovigilance activity HELP extension Study DX-2930-04 is acceptable for further characterising the safety concerns.

There are no additional risk minimisation activities beyond the inclusion of the CMI as a package insert. This is acceptable given the nature of the safety concerns.

### New and outstanding recommendations from second round evaluation

The sponsor’s commitment to include the CMI in the package is satisfactory. Given the complexity of the self-administration instructions, it is recommended to the Delegate that the commitment to include the CMI in the package be made a condition of registration.

The sponsor states that the following wording relating to the important identified risk of ‘hypersensitivity’ was included in the Summary of Product Characteristics SmPC to comply with EU guideline requirements and was not specific to Takhzyro. The sponsor has chosen not to include it in the PI on the grounds that it is not a mandatory requirement for PI documents in Australia. It is recommended that the Delegate review from a clinical perspective the importance of including the following SmPC wording in the PI to address the important identified risk of hypersensitivity:

It is strongly recommended that every time lanadelumab is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

<sup>32</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Missing information on long term safety in paediatric population and long term safety in adult population does not appear to be mentioned in the PI. The sponsor has declined the RMP evaluation recommendation to include this in the PI on the basis that there is no demonstrated risk at this time. It is recommended to the delegate that wording be included in the PI to communicate that long term safety has not been studied in the paediatric or adult populations.

### **Proposed wording for conditions of registration**

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The lanadelumab EU-Risk Management Plan (RMP) (version 1.3, dated 9 October 2018, data lock point 1 September 2017), with Australian Specific Annex (version 1.1, dated 12 October 2018), included with submission PM-2018-01464-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the periodic safety update report (PSUR) requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Takhzyro is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Lanadelumab (Takhzyro) is to be included in the Black Triangle Scheme. The PI and CMI for Takhzyro must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

## **VII. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations.

## Introduction

Hereditary angioedema (HAE) is a rare condition. Based on the registry data, the ASCIA estimate the prevalence in the Australian population to be 0.18 per 100,000 persons.

Hereditary angioedema is caused by mutations in the gene encoding the C1 esterase inhibitor (C1-INH). Three types of HAE have been described:

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

There are a variety of triggers for episodes of angioedema. Stress (either mental or physical) and dental procedures are the most common. Untreated, about one third of attacks are estimated to result in death.

Treatment options have rapidly expanded in the past decade. The TGA has approved two human plasma derived forms of C1-INH concentrate, Cinryze and Berinert for treatment of acute attacks, with Cinryze also approved for short and long term prophylaxis. The preparation for SC administration, Berinert SC, has been recently approved by the TGA for the prophylaxis of HAE attacks. Oral tranexamic acid and danazol have been approved by the TGA for use in HAE.

The regulatory status of the newer acute attack treatments is as follows:

- recombinant C1-INH, conestat-alfa, has been approved by the FDA and the EMA, but not the TGA to date;
- icatibant, a selective competitive antagonist at the bradykinin B2 receptor, has been approved by the TGA, EMA and FDA, treatment of acute attacks of HAE in adults;
- ecallantide, a pK<sub>1</sub> inhibitor, has only received approval from the FDA for treatment of acute attacks of HAE in patients 12 years of age and older.

## Overseas regulatory status for lanadelumab

### ***United States Food and Drug Administration (US FDA)***

Lanadelumab was approved by the FDA on 23 August 2018. The approved indication and dose recommendation are as follows:

*Takhzyro is a plasma kallikrein inhibitor (monoclonal antibody) indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.*

*Recommended dose:* administer 300 mg every two weeks. Dosing every 4 weeks is also effective and may be considered if the patient is well controlled for more than 6 months.

### ***Health Canada***

Health Canada authorised Takhzyro for routine prevention of attacks of HAE on September 19, 2018. According to the product monograph, the wording of the approved indication is:

*Takhzyro (lanadelumab injection) is indicated for routine prevention of attacks of hereditary angioedema (HAE) in adolescents and adults. Takhzyro is not intended for acute treatment of HAE attacks.*

*Recommended dose:* is the same as that approved by the FDA.

## **EMA**

The EMA's Committee on Medicinal Products for Human Use (CHMP) issued a positive opinion on 18 October 2018 for lanadelumab, supporting the following indications and dose recommendations:

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

*Recommended dose:* The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.

*EU presentation:* Takhzyro 300 mg solution for injection (1 vial of 2 mL).

The sponsor states that the clinical and nonclinical data set included in the Australian submission is essentially identical to that submitted to the USA, EU (via the centralised procedure), Canada and Switzerland.

## **Quality**

Lanadelumab is a recombinant human IgG1 kappa mAb that consists of two light chains (213 residues) and two heavy (451 residues) chains.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of lanadelumab have been controlled to an acceptable level.

There are no objections to the registration of this product from sterility; endotoxin, container safety and viral safety related aspects.

## **Nonclinical**

The submitted nonclinical data were in general accordance with the ICH guideline on the non-clinical evaluation of biotechnology-derived pharmaceuticals.<sup>2</sup> All pivotal repeat dose toxicity and reproductive toxicity studies were GLP compliant.

*In vitro*, lanadelumab inhibited human pKal without activity to prekallikrein or tissue kallikreins. Clinically significant off-target activities are unlikely and no safety concerns were identified. No major toxicities were observed in repeat dose studies in rats or cynomolgus monkeys. There was no evidence of teratogenicity in primates.

There are no nonclinical objections to the registration of lanadelumab for the proposed indication. The sponsor has accepted the changes to the PI statements as recommended by the nonclinical evaluator.

## **Clinical**

The submission includes the following study reports:

- Reports of biopharmaceutic studies with listing of:
  - 26 bioanalytical and analytical methods for human studies

- Clinical study reports for:
  - § Study DX-2930-01: Healthy subject pharmacokinetic and initial tolerability study
  - § Study DX-2930-02: HAE patient pharmacokinetic and initial tolerability study
  - § Study DX-2930-03: The main efficacy study for the proposed indication
  - § Study DX-2930-04: An open label extension study for DX-2930-03.
- Population pharmacokinetic reports, with these listed as:
  - Population pharmacokinetic, pharmacokinetic/pharmacodynamic and exposure-response analysis of SHP643 (DX-2930) for long term prophylaxis against acute attacks of hereditary Angioedema (Part 1 and Part 2)
  - A separate analysis plan was provided for each population pharmacokinetic report.
- Other reports included:
  - Potential for cardiovascular effects of plasma kallikrein inhibitors: a review of the literature and of data from Study DX-2930-03
  - Lanadelumab QT evaluation plan assessment
  - ECG assessment report for Study DX-2930-03 and Study DX-2930-04
  - Review of lanadelumab (DX-2930) hepatic events in Phase III studies
  - Paediatric data: Lanadelumab (SHP643, DX-2930)
  - Evidence supporting the Angioedema Quality of Life (AE-QoL) questionnaire in patients with HAE
- Literature references with 106 publications listed.

### Pharmacokinetics

Clinical pharmacokinetic investigations were limited to measurements of plasma lanadelumab concentration after single or repeated dosing. No investigations of distribution, metabolism or excretion have been performed. Measurement of plasma lanadelumab was by two different assays, both of which are reported to measure free lanadelumab. Cross-validation of the assays was not performed. One assay was used in the study of healthy subjects. A different assay was used in the three studies of HAE patients.

The lanadelumab pharmacokinetic in healthy subjects was found to differ from that in HAE patients, with lower clearance and longer half-life. The pharmacokinetic profile in HAE patients, as demonstrated in Study DX-2930-02, was characterised by:

- slow absorption that was independent of dose. The average time to peak plasma concentration was between 3 and 8 days;
- exposure, as shown by measures of AUC, was dose-dependent;
- clearance was linear and independent of dose;
- prolonged half-life that was independent of dose;
- low distribution that was independent of dose.

There were no dedicated pharmacokinetic studies to investigate the effects of race, renal impairment, hepatic impairment or special populations. There were no dedicated investigations of drug-drug interactions. The proposed PI statements regarding pharmacokinetics in special groups and drug-drug interactions are based on the

population pharmacokinetic analyses and additional post hoc analyses. The evaluator has concerns regarding the validity of the pharmacokinetic model and its predictive ability as development of the model has assumed that the plasma lanadelumab concentrations measured by the two different assays are interchangeable and given that it has predicted lower exposure with every 2 weeks regimen compared to every 4 weeks regimen. The population pharmacokinetic analyses regarding special populations were also limited by the small numbers of participants in many of the sub-groups.

The evaluator is of the opinion that weight-based (body weight) dosing should be considered. The population pharmacokinetic analyses found that lower body weight was associated with higher lanadelumab exposure. Population pharmacokinetic/pharmacodynamic analyses have also demonstrated that the mean concentrations achieved with all three regimens (in the pivotal study) are, in general, considerably in excess of the IC<sub>50</sub> needed to achieve the pharmacodynamic end-points of pKal inhibition and reduction in monthly attack rate. Assuming that these are real findings, and given that the pivotal study could not demonstrate any significant difference in efficacy between the three regimens, then there would appear to be no need to administer the same dose to patients with lower body weight. The sponsor proposes that the recommended dose in all patients should be 300 mg every 2 weeks. The evaluator recommends that the dose of 150 mg should be considered the preferred dose in patients of lower body weight, including adolescents.

### **Pharmacodynamics**

Pharmacodynamic data has been included from each of the three clinical trials in HAE patients and from the first-in-human study in healthy subjects. The exploratory biomarkers, activity of pKal and cleaved HMWK level, were used to investigate pharmacodynamic effects. Overall, the pharmacodynamic data support the purported mechanism of action. The biological actions of pKal inhibition with reduced cleaved HMWK production were demonstrated. It is plausible that these actions will result in reduced bradykinin production and reduced HAE attacks.

Pharmacokinetic/pharmacodynamic analyses demonstrated a greater reduction in the average monthly HAE attacks in lanadelumab treated patients compared to placebo treated patients. The process of pKal inhibition by lanadelumab appears to be saturated at the concentrations seen with the dosing regimens proposed for approval, with no significant difference in the reduction in cleaved HMWK level or average monthly HAE attack rate evident across the 3 regimens investigated in the Phase III study.

The limited investigation of secondary pharmacodynamic effects found no effects of lanadelumab on ECG parameters; mild prolongation of aPTT without associated bleeding; and low immunogenicity. No pharmacodynamic drug interaction studies were conducted.

### **Efficacy**

The sponsor has presented Study DX-2930-03 as pivotal for efficacy, with the open label extension Study DX-2930-04 described as supportive. The Phase Ib Study, DX-2930-02, was presented as providing 'proof-of-concept'. Efficacy analyses in the studies were all based on some measure of acute HAE attacks. This is appropriate and consistent with studies investigating other long term prophylactic treatments for HAE.

#### ***Study DX-2930-03***

The main efficacy study, Study DX-2930-03, was a Phase III, multicentre, randomised, double blind, placebo controlled, parallel group trial that assessed three regimens (150 mg every 4 weeks, 300 mg every 4 weeks and 300 mg every 2 weeks) over a 26 week period. The study enrolled patients with confirmed HAE type I or II who were aged 12 years or older and who had a demonstrated baseline HAE attack frequency of 1 per month. Patients



who were already receiving long term prophylaxis could enrol but only after cessation of this therapy and a washout period. The primary efficacy endpoint was the rate of investigator-confirmed HAE attacks during the treatment period. Secondary endpoints were of other measures of HAE attacks. There were 125 participants, randomised as follows: placebo (n = 41); 150 mg every 4 weeks (n = 28); 300 mg every 4 weeks (n = 29); 300 mg every 2 weeks (n = 27). The result of primary endpoints is presented in Table 26.

**Table 26: Results of primary efficacy endpoints from pivotal Study DX-2930-03**

| Efficacy Endpoints   | Efficacy Results by Treatment Arm |                             |                             |
|--|-----------------------------------|-----------------------------|-----------------------------|
|  | Lanadelumab                       |                             |                             |
|  | 150 mg q4wks                      | 300 mg q4wks                | 300 mg q2wks                |
| Number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182)<br>%Change (95% CI)<br>(see Table 2)  | -75.6<br>(-84.650, -61.243)       | -73.3<br>(-82.379, -59.456) | -86.9<br>(-92.828, -76.150) |
| Number of investigator-confirmed HAE attacks during the estimated steady state period, Day 70 through Day 182.<br>%Change (95% CI)<br>(see Figure 5)   | -77.6<br>(-86.702, -62.314)       | -80.6<br>(-88.466, -67.326) | -91.5<br>(-96.132, -81.129) |
| Negative Binomial GLM Analysis (sensitivity analysis) of number of investigator-confirmed HAE attacks during the treatment period.<br>%Change (95% CI)<br>(Module 5.3.5.1, Study DX-2930-03 CSR, Table 18) | -74.2<br>(-83.946, -58.412)       | -75.1<br>(-84.385, -60.392) | -86.8<br>(-92.169, -77.683) |

CI=confidence interval; GLM=generalized linear model; HAE=hereditary angioedema

Note: Comparison to placebo; all p-values <0.001.

The study met its primary endpoint with a reduction in investigator confirmed HAE attack rates during the treatment period compared to placebo of more than 70% for each of the treatment arms ( $p < 0.001$ ). Analyses of HAE attacks requiring acute treatment, laryngeal attacks and high morbidity attacks found that these more severe attacks were similarly reduced, indicating that the reduction is not limited to minor HAE attacks. Also of importance is that a higher percentage of subjects (31.0% to 44.4%), in the 3 treatment arms were 'attack-free' compared to placebo (2.4%) throughout the 26 week treatment period.

Robustness of the results was demonstrated as the results for secondary efficacy endpoints, sensitivity and most sub-group analyses were all consistent with the result for the primary end-point. No distinction can be made regarding efficacy for the three regimens. There were some minor numerical differences in results across the treatment arms but these were not consistent and the study was not designed or powered to compare the treatment effect within the three lanadelumab treatment arms.

#### **Study DX-2930-04**

The open label extension study (OLE), Study DX-2930-04, was included as supportive of efficacy. This study enrolled patients from all treatment arms of Study DX-2930-03, with 109 of 125 participants electing to continue into the OLE (rollover patients). Participants who were not part of Study DX-2930-03 could also participate (non-rollover patients). A lower rate of baseline HAE attacks was accepted for these patients. Treatment regimens differed between the rollover and non-rollover patients: rollover patients received a single dose of lanadelumab and then commenced a dose-and-wait phase with lanadelumab 300 mg every 2 weeks commenced with the first HAE attack; non-rollover patients commenced lanadelumab 300 mg every 2 weeks from study entry. The study enrolled 109 rollover patients and 103 non-rollover patients, including 19 patients from Study DX-2930-02.

Interpretation of the results of this study is limited by the absence of a placebo arm, open label administration, inclusion of groups with differing baseline attack rates and different treatment approaches. Given these factors, this study can provide limited support. However, the range of median attack rates during the treatment periods of lanadelumab 300 mg q2w was between 0.0 and 15.4 attacks per month and consistent with the rates reported in the main efficacy study. Rollover patients from active treatment arms in Study DX-2930-03 achieved similar control according to mean HAE attack rates as were



achieved in the earlier study, suggesting that the break in treatment during the dose-and-wait phase did not affect efficacy on treatment resumption. There were 70 patients with 1 year of cumulative experience (inclusive of the dose-and-wait period) across Studies DX-2930-03 and DX-2930-04. Median HAE attack rates achieved with lanadelumab in Study DX-2930-03 were maintained during Study DX-2930-04, suggesting that tolerance over this period of time does not develop. However, there were 3 participants in Study DX-2930-03 who were categorised as responders in this study and who were categorised as non-responders in Study DX-2930-04. This was attributed to the occurrence of life-changing stressful events triggering HAE attacks, rather than the development of tolerance.

### ***Study DX-2930-02***

This Phase Ib study provided proof of concept. The analysis of those HAE participants who received two doses of 300 mg or 400 mg of lanadelumab and who had a baseline attack rate of at least 2 attacks in the 3 months found a 100% reduction in HEA attacks versus placebo for 300 mg lanadelumab ( $p < 0.0001$ ) and an 88% reduction versus placebo for 400 mg lanadelumab ( $p = 0.005$ ). The numbers analysed were small: lanadelumab 300 mg  $n = 4$ ; lanadelumab 400 mg  $n = 11$ ; placebo  $n = 11$ .

### **Safety**

The exposure of lanadelumab is limited to 257 unique individuals, with these comprising 24 healthy subjects who received a single dose of lanadelumab and 233 patients with HAE type I or II who have received a variety of regimens. There have been only 57 patients who have received treatment for 12 months or more.

Clinical experience with lanadelumab is limited. However, it appears to be well tolerated at the dosing regimens that were found to have efficacy (150 mg every 4 weeks, 300 mg every 4 weeks and 300 mg every 2 weeks) and with no apparent evidence of dose related toxicity.

There were no deaths reported in any of the studies. SAEs were infrequent and, in general, according to the narratives provided, unlikely to be due to lanadelumab. Treatment discontinuations due to AEs were also rare, but did include AEs related to lanadelumab, including hypersensitivity reactions and elevated transaminases.

In Study DX-2930-03, AEs were reported in 76% of the patients in the placebo arm and 90% of the patients in the lanadelumab arms. The AEs that were reported more frequently in lanadelumab treated patients were largely those due to injection site reactions (46% versus 26%) with these including pain, erythema, bruising, discomfort, swelling, haematoma, and haemorrhage. Similar high rates of injection site reactions were reported in Study DX-2930-04. Dizziness was reported more commonly in the lanadelumab treated patients in Study DX-2930-03 but was not consistently reported across the other studies. Headache was reported in similar proportions of lanadelumab treated and placebo treated patients.

The clinical evaluator has made the following comments about the safety, but has cautioned about the small number of patients for which these conclusions are based upon:

- Safety evaluation in patients in whom lanadelumab was recommenced after a treatment break of as long as 2 years identified no additional safety concerns, including no increased risk of the development of antidrug antibodies or hypersensitivity reactions.
- Safety analysis in a small number of patients receiving lanadelumab concurrent with other long term prophylaxis therapy/therapies, whilst the latter were being weaned also identified no additional safety concerns.

- An analysis of AEs according to duration of therapy did not identify specific concerns although there appeared to be an increase in the proportion of patients in whom AEs were reported with increasing duration of treatment.
- Self-administration by trained patients/carers was evaluated in Study DX-2930-04 and was not found to result in an increase in injection site reactions. Other measures of safety with self-administration were not specifically reported.
- Testing for antidrug antibodies in the clinical studies found low rates of antidrug antibodies positivity, with this commonly transient, of low titres, usually non-neutralising and not associated with any apparent differences in safety or efficacy.
- A separate presentation of safety in adolescents indicated that safety in this group was similar to that of the overall population.

In terms of hypersensitivity reactions, there were no events of anaphylaxis or anaphylactoid reactions reported. The hypersensitivity reactions that were reported were minor and included symptoms of tingling, itchiness, discomfort, headache and peripheral joint pain. In 2 patients, treatment was discontinued. In one patient, this comprised peripheral joint pain and oedema that was treated with corticosteroids. In the other, the event consisted of a small area of maculopapular erythematous dermatitis that was itchy and close to the injection site and occurred with both the first and second dose of lanadelumab. These reactions were not related to the development of antidrug antibodies.

The following safety signals have been identified by the evaluator:

- Injection site reactions, with localised hypersensitivity reactions (including rash) resulting in treatment discontinuation in 2 patients. Pain, bruising and bleeding at the injection site were more common in lanadelumab treated subjects.
- Elevated transaminases consisting of asymptomatic elevations in up to 5% of lanadelumab treated patients. There have been no Hy's law cases or reports of severe liver injury or liver failure. It has been managed by discontinuation, temporary treatment cessation. The mechanism of injury is unknown.
- Creatinine kinase elevation with this consisting of low-grade elevation in around 6% of patients and marked elevation, most commonly following exercise, in a small number. Two patients discontinued treatment due to marked elevation (together with AST and ALT elevation). There were no reports of rhabdomyolysis or SAEs related to creatinine kinase elevation. The mechanism of injury is unknown.
- Disordered coagulation is a theoretical concern with lanadelumab and clotting tests were monitored during the clinical studies. Mild increases, particularly in aPTT, were reported in a small number of patients. There did not appear to be an increased overall bleeding risk. However, the possibility of an increased local bleeding risk is suggested by the higher rate of injection site bleeding and bruising reported in lanadelumab treated patients compared to placebo patients.

Overall, lanadelumab appears to be well-tolerated and to not be associated with serious adverse effects to date. However, it must be recognised that only small number of patients have been exposed and only for relatively short periods of time given that it is proposed for long term use.

## Risk management plan

It is noted that an updated EU-RMP version 1.3 (9 October 2018; data lock point 1 September 2017) with the ASA version 1.1 (12 October 2018) have been submitted with the sponsor's post-first round response. The proposed summary of safety concerns and

their associated risk monitoring and mitigation strategies are summarised in Table 25 above.

## Risk-benefit analysis

More information and documents have been provided to the TGA after the completion of the second round TGA evaluations. These include CHMP responses, CHMP positive opinion, and the proposed EU SmPC. These documents are provided for the Advisory Committee on Medicines (ACM) meeting.

The wording of the indications and dose recommendations are the two issues for which the ACM advice is specifically sought.

## The wording of the indication

### *Type of HAE*

The evaluator recommends the following wording for the indications:

*Takhzyro is indicated for routine prevention of angioedema attacks in patients aged 12 years and older with ~~and the control of symptoms of~~ hereditary angioedema (C1-esterase inhibitor deficiency or dysfunction C1-INH) who have frequent severe attacks and who are inadequately controlled by on-demand treatments.*

The sponsor agrees to the removal of 'control of symptoms', but does not accept a limitation to HAE with deficient or dysfunctional C1-INH and with frequent severe attacks who are inadequately controlled by on-demand treatments.

The evaluator argues that only patients with HAE with deficient or dysfunctional (types I or II) could participate in the studies. Patients with HAE type III were not included. Subgroup analysis in Study DX-2930-03 found that efficacy was demonstrated in patients with HAE type I, and there were only 12 patients with HAE type II. The evaluator recognises that there were only a small number of patients with HAE type II but is of the opinion that it is reasonable to extrapolate to HAE type II, given their similar pathophysiology and given that it is generally accepted practice to group the two types together in clinical guidelines.

The sponsor acknowledged that the pathophysiology of HAE with normal C1-INH (formerly known as type III) is yet to be fully understood. The sponsor provided some speculations regarding the pathophysiology of HAE type III and argues that the plasma kallikrein-kinin system, with unregulated pKal and excess bradykinin is also key to this. On this basis, the sponsor argues that the prevention treatment effects of lanadelumab could be extrapolated to HAE with normal C1-INH.

However, the evaluator notes that it is evident from clinical guidelines, funding and regulatory bodies that HAE with normal C1-INH is not considered the same disease as HAE with deficient or dysfunctional C1-INH. The evaluator notes that nomenclature in HAE is rapidly evolving, with the most recent revision of the International WAO/EAACI guideline for the management of HAE (published January 2018);<sup>33</sup> recognising five different forms of HAE. As a consequence, terminology that refers to the pathophysiological process or underlying genetic mutation is now preferred. The evaluator considers that it would be most appropriate for the wording of the indication refer to 'deficiency/dysfunction of C1 esterase inhibitor'.

<sup>33</sup> Maurer et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *World Allergy Organization Journal* (2018) 11:5 DOI 10.1186/s40413-017-0180-1

**Frequent severe attacks**

The sponsor does not agree to limit the indication to HAE patients who have frequent severe attacks who are inadequately controlled by on-demand treatments, and argues that lanadelumab has shown to be effective in patients with less frequent and/or less severe attacks, and limiting its use to patients with frequent severe attacks will deny a feasible preventive option for other patients.

The Delegate noted that the inclusion criteria in Study DX-2930-03 requires a baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks, that is a subset of HAE subjects with recurrent attacks, and a history of recurrent attacks was a requirement for inclusion in all three studies (Studies DX-2930-02, DX-2930-03, and DX-2930-04). The delegate agrees with the CHMP and considers that the benefit/risk ratio is considered positive only for subjects with recurrent HAE attacks, not for subjects with only one attack or very rare attacks. The delegate therefore proposes to limit the indication to HAE subjects with recurrent HAE attacks. The ACM advice is sought on the exact wording of the Indications.

The sponsor submitted a revised PI on 01 November 2018. The indications have been revised to the following:

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

**Dose recommendations**

The evaluator is of the view that the optimal dosing regimen has not been determined as the pivotal study was not designed to compare the treatment effect within the three randomized lanadelumab treatment arms. The evaluator considers that the small numerical differences in the three arms in Study DX-2930-03 reflect small numbers and the inherent intra-individual variability in the pattern of HAE attacks rather than greater efficacy with one arm, and there is insufficient data to recommend any one regimen over the other two dose regimens. The evaluator considers that it is reasonable to consider individualised care by treating specialist and proposes 'weight adjusted dosing' and 'treatment interruption'. The dose recommendations proposed by the Evaluator at the second round are as follows:

- The optimal dose and dose frequency have not been established. The following regimens were found to have similar efficacy in the HELP study: 150 mg every 4 weeks, 300 mg every 4 weeks and 300 mg every 2 weeks.
- Consideration should be given to commencing patients with body weight greater than 100 kg on the dose of 300 mg and patients with body weight less than 50 kg on the dose of 150 mg.
- Treatment interruption may be considered after 6 months of continuous prophylactic treatment in well-controlled patients (for example, attack free), with Takhzyro treatment to be recommenced with the first HAE attack.

The evaluator's rationale for the proposed dose recommendations have been discussed in detail in the clinical evaluation report.

The Delegate agrees that the pharmacokinetic analyses suggest a lower exposure in subjects with higher body weight and a higher exposure in subjects with low weight. It is relevant to review whether the heavier subjects had been effectively managed with the highest dose (300 mg every 2 weeks) and whether the lighter subjects were more at risk of having treatment emergent AEs. The Delegate reviewed the subgroup analysis by patients' weight and noted that the 300 mg every 2 weeks regimen demonstrated the effect in reducing HAE attack rate for all weight groups (including body weight  $\geq$  100 kg)

while 150 mg every 4 weeks regimen did not appear to have the effect on HAE attack rate in subjects with body weight  $\geq 100$  kg. The effect of the three regimens in subject's  $\geq 100$  kg in Study DX-2930-03 is presented in the tables below. A significant mean reduction in HAE attack rate was observed for 300 mg every 2 weeks regimen in comparison to placebo as well as to the run-in period attack rate. The small number of subjects in each group is noted.

**Table 27: Poisson regression of investigator-confirmed HAE attacks during the treatment period (Day 0 to Day 182) by weight group and treatment group (intent to treat population)**

| Statistic  | Weight Category: $<50$ kg (N=3) |  |  |  |
|--|---------------------------------|--|--|--|
|  | Placebo<br>N=2                  | DX-2930 150 mg every<br>4 weeks<br>N=0 | DX-2930 300 mg every<br>4 weeks<br>N=1 | DX-2930 300 mg every<br>2 weeks<br>N=0 |
| Run-in Period HAE Attack Rate (attacks/month) [a]    |                                 |  |  |  |
| n  | 2                               | 0                                      | 1                                      | 0                                      |
| Mean (SD)  | 0.983 (0.024)                   |  | 0.966                                  |  |
| Median   | 0.98                            |  | 0.97                                   |  |
| Min, Max   | 1.0, 1.0                        |  | 1.0, 1.0                               |  |
| Treatment Period HAE Attack Rate (attacks/month) [a] |                                 |  |  |  |
| n  | 2                               | 0                                      | 1                                      | 0                                      |
| Mean (SD)  | 0.228 (0.323)                   |  | 0.459                                  |  |
| Median   | 0.23                            |  | 0.46                                   |  |
| Min, Max   | 0.0, 0.5                        |  | 0.5, 0.5                               |  |
| HAE Attack Rate Model Analysis [b]                   |                                 |  |  |  |
| Estimated LS Mean Rate (attacks/week) (SE)           |                                 | NE                                     | NE                                     | NE                                     |
| 95% CI of Rate (attacks/week)                        |                                 | NE                                     | NE                                     | NE                                     |
| Estimated LS Mean Rate (attacks/month) (SE)          |                                 | NE                                     | NE                                     | NE                                     |
| 95% CI of Rate (attacks/month)                       |                                 | NE                                     | NE                                     | NE                                     |
| Rate Ratio (vs Placebo)                              |                                 | NE                                     | NE                                     | NE                                     |
| 95% CI of Rate Ratio                                 |                                 | NE                                     | NE                                     | NE                                     |
| p-value Unadjusted [c]                               |                                 | NE                                     | NE                                     | NE                                     |

[a] A month is defined as a 4 week period or 28 days.

[b] Results from Poisson regression model with fixed effects for treatment group (categorical) and normalized baseline attack rate (continuous), and logarithm of time in days each subject was observed during treatment period as offset variable in model. Pearson chi-square scaling of standard errors was employed to account for potential overdispersion. Mean estimates are Least Squares (LS) means.

[c] Unadjusted p-values are derived from Poisson modeling.

[d] % change in mean rate corresponds to  $100\% \times (\text{estimated mean rate ratio} - 1)$ .

Poisson regression model outputs were suppressed for the treatment arms with only one subject.

NE=Non-estimated.

**Table 28: Number of confirmed HAE attack in subjects with bodyweight  $\geq 100$  kg in treatment period in Study DX-2930-03**

|  | Weight group<br>$\geq 100$ kg (N=21) |                                      |                                      |                                      |
|--|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
|  | Placebo<br>(N=6)                     | Lanadelumab<br>150 mg q4wks<br>(N=2) | Lanadelumab<br>300 mg q4wks<br>(N=4) | Lanadelumab<br>300 mg q2wks<br>(N=9) |
| Baseline attack rate, mean (SD)                              | 3.72 (2.82)                          | 5.85 (0.73)                          | 4.23 (2.15)                          | 3.83 (2.60)                          |
| Treatment period HAE attack rate, mean (SD)                  | 1.54 (0.76)                          | 1.45 (0.75)                          | 0.60 (0.49)                          | 0.27 (0.40)                          |
| LS Mean (95% CI) monthly attack rate                         | 1.57 (0.99, 2.49)                    | 1.32 (0.49, 3.53)                    | 0.61 (0.24, 1.53)                    | 0.27 (0.11, 0.66)                    |
| % Reduction in mean attack rate relative to placebo (95% CI) |                                      | 16%<br>(-151.41, 72.01)              | 61%<br>(-8.45, 86.17)                | 83%<br>(52.91, 93.65)                |



**Table 29: Number of investigator-confirmed HAE attack by weight and treatment group in treatment period in Studies DX-2930-03 and DX 2930-04**

|  | Study DX-2930-03<br>(pivotal efficacy study)<br>ITT Population |                                       |                                       |                                       | Study DX-2930-04<br>(supportive efficacy study)<br>Rollover Safety Population |  |  |  |
|--|--|---------------------------------------|---------------------------------------|---------------------------------------|---|--|--|--|
|  | Treatment  |                                       |                                       |                                       | Current treatment<br>(Prior treatment)  |  |  |  |
| Weight group<br>50 to <75 kg                   |  |                                       |                                       |                                       |   |  |  |  |
|  | Placebo<br>(N=24)  | Lanadelumab<br>150 mg q4wks<br>(N=12) | Lanadelumab<br>300 mg q4wks<br>(N=13) | Lanadelumab<br>300 mg q2wks<br>(N=10) | Lanadelumab<br>300 mg q2wk<br>(Placebo)<br>(N=19)                             | Lanadelumab<br>300 mg q2wk<br>(150 mg q4wks)<br>(N=11) | Lanadelumab<br>300 mg q2wk<br>(300 mg q4wks)<br>(N=12) | Lanadelumab<br>300 mg q2wks<br>(300 mg q2wk<br>(N=9) |
| Baseline attack rate,<br>mean (SD)             | 3.79<br>(2.285)  | 2.57<br>(1.428)                       | 2.69<br>(1.891)                       | 2.59<br>(2.175)                       | 3.72 (2.417)  | 2.72 (1.404)   | 2.76 (1.963)   | 2.30 (2.085)   |
| Treatment period HAE<br>attack rate, mean (SD) | 2.40<br>(1.758)  | 0.32<br>(0.604)                       | 0.38<br>(0.390)                       | 0.23<br>(0.516)                       | 0.58 (1.146)  | 0.14 (0.276)   | 0.36 (0.615)   | 0.00 (0.000)   |
| Weight group<br>75 to <100kg                   |  |                                       |                                       |                                       |   |  |  |  |
|  | Placebo<br>(N=9)   | Lanadelumab<br>150 mg q4wks<br>(N=14) | Lanadelumab<br>300 mg q4wks<br>(N=11) | Lanadelumab<br>300 mg q2wks<br>(N=8)  | Lanadelumab<br>300 mg q2wk<br>(Placebo)<br>(N=7)                              | Lanadelumab<br>300 mg q2wk<br>(150 mg q4wks)<br>(N=14) | Lanadelumab<br>300 mg q2wk<br>(300 mg q4wks)<br>(N=9)  | Lanadelumab<br>300 mg q2wks<br>(300 mg q2wk<br>(N=7) |
| Baseline attack rate,<br>mean (SD)             | 5.51<br>(5.317)  | 3.38<br>(1.927)                       | 4.96<br>(2.825)                       | 4.31<br>(2.061)                       | 4.85 (4.453)  | 3.39 (1.927)   | 4.77 (3.105)   | 4.52 (2.137)   |
| Treatment period HAE<br>attack rate, mean (SD) | 3.69<br>(2.961)  | 0.47<br>(0.546)                       | 0.87<br>(1.181)                       | 0.44<br>(0.623)                       | 0.17 (0.260)  | 0.23 (0.319)   | 0.79 (0.807)   | 0.29 (0.392)   |
| Weight group<br>≥100kg                         |  |                                       |                                       |                                       |   |  |  |  |
|  | Placebo<br>(N=6)   | Lanadelumab<br>150 mg q4wks<br>(N=2)  | Lanadelumab<br>300 mg q4wks<br>(N=4)  | Lanadelumab<br>300 mg q2wks<br>(N=9)  | Lanadelumab<br>300 mg q2wk<br>(Placebo)<br>(N=5)                              | Lanadelumab<br>300 mg q2wk<br>(150 mg q4wks)<br>(N=1)  | Lanadelumab<br>300 mg q2wk<br>(300 mg q4wks)<br>(N=3)  | Lanadelumab<br>300 mg q2wks<br>(300 mg q2wk<br>(N=9) |
| Baseline attack rate,<br>mean (SD)             | 3.72<br>(2.821)  | 5.84<br>(0.729)                       | 4.22<br>(2.153)                       | 3.83<br>(2.599)                       | 3.79 (3.148)  | 5.33 (NA)  | 3.86 (2.478)   | 3.83 (2.599)   |
| Treatment period HAE<br>attack rate, mean (SD) | 1.54<br>(0.755)  | 1.45<br>(0.749)                       | 0.59<br>(0.494)                       | 0.27<br>(0.403)                       | 0.13 (0.187)  | 0.14 (NA)  | 0.25 (0.220)   | 0.33 (0.303)   |

In Study DX-2930-04, the mean percent change from Baseline in HAE attack rate in non-rollover subjects  $\geq 100$  kg ( $n = 21$ ) was 87.0%, which was comparable with the other weight groups (93.5%, 68.9% and 89.2% for weight  $< 50$  kg, 50 to  $< 75$  kg, and 75 to  $< 100$  kg, respectively).

The pharmacokinetic/pharmacodynamic analysis showed that the 300 mg every 2 weeks dosing was associated with lanadelumab exposure approximate or above the 90% inhibitory concentration ( $IC_{90}$ ) of pharmacodynamics and effective area under the curve associated with 90% of the maximum effect  $EAUC_{90}$  for efficacy in patients across a large range of body weight (46.8 to 150 kg).

Taking the above analysis into consideration, the 300 mg every 2 weeks regimen is effective for subjects with all weight ranges, including subjects with body weight  $\geq 100$  kg and a special dosing for heavy subjects is not considered needed.

TEAEs were examined by the subsets of age ( $< 18$ , 18 to  $< 40$ , 40 to  $< 65$ ,  $\geq 65$  years), gender, race (white, other), and weight ( $< 50$ , 50 to  $< 75$ , 75 to  $< 100$ ,  $\geq 100$  kg) in subgroup analyses for the lanadelumab treated population. Despite the small sample sizes within some of the subsets, there were no clinically meaningful differences observed in the safety profile of lanadelumab when analysed by age, gender, race, or weight. The relationship between lanadelumab exposure and different safety parameters did not show strong correlations between drug exposure and liver function tests, cardiovascular parameters, haematological parameters (including aPTT), respectively.

Safety profile for subjects with body weight  $< 50$  kg: there were a total of 7 subjects  $< 50$  kg who were treated with lanadelumab in the two studies. In Study DX 2930-03, two subjects  $< 50$  kg were treated with placebo and one subject with lanadelumab 300 mg every 4 weeks. All 3 subjects rolled over to Study DX-2930-04 and were treated with lanadelumab 300 mg every 2 weeks. In Study DX-2930-03, two TEAEs were reported by the lanadelumab treated subject and non by the placebo subjects. None of the TEAEs was considered related to treatment and none was serious or severe. In Study DX-2930-04, the rate of related treatment emergent AEs/ per subject year was higher in the  $< 50$  kg

subgroup compared to other subgroups. It is however noted that in the < 50 kg subgroup, 3 subjects reported 67 related treatment emergent AEs which were all injection site reactions. No AE of special interests or serious or severe AE were reported in subjects < 50 kg.

Taking into account the safety profile for subjects < 50 kg, the general benign safety profile of lanadelumab, the efficacy of lanadelumab 300 mg every 2 weeks for subjects with all weight groups, the risk of medication error and self-injection difficulties associated with the variable dose regimens, the Delegate inclines to accept the rationale presented by the CHMP and also the following dose recommendations proposed by the CHMP:

The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.

It is noted that the EU applicant has decided to remove the 150 mg presentation from its application. This is in response to the CHMP Day 120 question regarding no proposed use for the 150 mg presentation.

## **Delegate's considerations**

### ***Summary of issues***

One pivotal and a number of supportive studies were submitted. The results from the pivotal study demonstrated evidence of efficacy with lanadelumab in preventing HAE attacks in HAE patients (types I and II) who had the history of recurrent HAE attacks. Three regimens (150mg Q4W, 300mg Q4W and 300mg Q2W) assessed in the pivotal study had all demonstrated the effect. Lanadelumab appears to be well-tolerated and to not be associated with serious adverse effects. However, it must be recognised that only small number of patients have been exposed and only for relatively short periods of time. There are different views between the evaluator and the sponsor with regards to the wording of the indications and the appropriate dose recommendations. These issues are discussed in detailed in the clinical evaluation report [not included with this AusPAR] and in the body of the Delegate's Overview (presented above).

Lanadelumab has now been approved by the FDA and Health Canada. The CHMP has issued a positive opinion. The indications and dose recommendations approved by these regulatory agencies are detailed in the body of this Overview (see above).

The Delegate is of the view that there is a favourable benefits risks balance for the use of lanadelumab in preventing HAE attacks. The ACM advice is sought on the appropriate wording of the indications and the dose recommendations.

### ***Conditions of registration***

1. Batch release testing and compliance with Certified Product Details (CPD) as detailed by the quality evaluator.
2. Conditions of registration from RMP aspects

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

‘The lanadelumab EU-Risk Management Plan (RMP) (version 1.3, dated 9 October 2018, data lock point 1 September 2017), with Australian Specific Annex (version 1.1, dated 12 October 2018), included with submission PM-2018-01464-1-2, and

any subsequent revisions, as agreed with the TGA will be implemented in Australia.'

3. In addition, as TAKHZYRO is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration.

'Lanadelumab (TAKHZYRO) is to be included in the Black Triangle Scheme. The PI and CMI for Takhzyro must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.'

### **Proposed action**

There is no reason to say, at this time, that the application for Takhzyro (lanadelumab) should not be approved. The exact wording of the indications and the dose recommendations will be determined following the ACM advice.

The Delegate proposes to approve the application to register Takhzyro (lanadelumab), subject to the finalisation of the wording of indications and the dose recommendations.

### **Request for ACM advice**

The committee is requested to provide advice on the following specific issues:

1. What is the advice of the committee with regards to the wording of the indications? Does the ACM consider that the indications should specify HAE patients with C1-INH deficiency or dysfunction who have frequent severe attacks and who are inadequately controlled by on-demand treatments?
2. What is the committee's advice with regards to the appropriate dosing recommendations?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

### **Response from sponsor**

Takhzyro (lanadelumab), a human IgG1 mAb inhibitor of active pKal, is proposed for the indication of routine prevention of recurrent attacks of HAE in patients aged 12 years and older.

Takhzyro has received accelerated review and marketing authorisation from major overseas regulatory authorities: the US FDA (approved 23 August 2018), Health Canada (approved 19 September 2018), and the EMA (positive CHMP opinion received on 18 October 2018; approval expected in December 2018) for the prevention of HAE attacks in patients aged 12 years and older.

The Delegate has asked the ACM for advice on the following matters:

- the wording of the indications: should the indications specify HAE patients with C1-INH deficiency or dysfunction who have frequent severe attacks and who are inadequately controlled by on-demand treatments;
- advice with regards to the appropriate dosing recommendations; and
- advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

In this response, the sponsor has responded to the matters raised by the Delegate.



### **Overview of the condition**

Hereditary angioedema (HAE) is a rare, serious, severely debilitating and life-threatening, and a highly variable genetic disease. It is estimated by the ASCIA that up to 480 cases could be expected to exist in Australia.<sup>34</sup> HAE manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal oedema of the face, larynx, gastrointestinal tract, limbs and/or genitalia. Patient's quality of life can be dramatically affected in light of the chronic, severely debilitating recurrent nature of HAE attacks and the ever present life-threatening risk of death from asphyxiation.

In view of the seriousness of the condition, and the currently unmet medical need for patients with HAE, Takhzyro was granted Priority Review by the TGA on 21 February 2018 based on its potential merit for prevention of HAE attacks.

### **Proposed indication**

The sponsor believes that there is a significant risk with the evaluator's suggested indication wording. Under the suggested indication, a patient would have to experience several potentially life-threatening attacks until the criteria for 'frequent severe attacks' (with inherent definitional ambiguity) was met before receiving effective preventative treatment. This is not aligned with the latest WAO HAE treatment guidelines;<sup>13</sup> which are endorsed by ASCIA, the goal for preventative treatment and the outcomes from lanadelumab clinical studies. On average, untreated individuals have an attack every 1 to 2 weeks, and most episodes last for about 3 to 4 days. The frequency, site and duration of attacks and triggers precipitating an attack are highly variable, even amongst affected family members. Given the clinical risk to patients if they are denied access to effective preventative treatment, it is critical to have a clear indication that lanadelumab is for routine prevention of recurrent HAE attacks.

Consistent with the currently approved preventative treatments for HAE, evaluation of routine prevention of recurrent attacks, not limited to only severe attacks, was the goal of the clinical studies with lanadelumab. In the pivotal Phase III Study DX-2930-03, although patients in all subgroups risk having a life-threatening angioedema attack, the magnitude of the treatment effect was the largest and most consistent across endpoints in the lanadelumab 300 mg every 2 weeks treatment arm compared to the lanadelumab every 4 weeks arms in all subgroups stratified by run-in period HAE attack rate (1 to < 2,  $\geq 2$  to < 3, and  $\geq 3$  per 4 weeks) to depict the severity spectrum of HAE disease. The supportive clinical studies in patients with HAE, Study DX-2930-04 and Study DX-2930-02, demonstrated the benefit/risk ratio for subjects with a history of < 1 HAE attack per 4 weeks is positive and consistent with other subjects with a history of  $\geq 1$  HAE attack per 4 weeks, therefore, lanadelumab should not be limited only for patients with frequent and/or severe attacks.

The safety profile of lanadelumab established from the results from the 26 week pivotal Phase III Study DX-2930-03 has been discussed in the application dossier. Furthermore, lanadelumab continues to be well tolerated, with the proportion of subjects discontinuing lanadelumab due to treatment emergent AEs remaining low (3.2%), as of the data cut of 1 January 2018 that provided 4 months of additional data after the interim data cut off on 1 September 2017 for the ongoing open label Phase III Study DX-2930-04. In total, 5843 doses of lanadelumab have been administered through a cut-off date of 01 Jan 2018 to 220 lanadelumab treated subjects, with an average of 26.6 doses of lanadelumab received per subject and a subject-time exposure of 240.1 years. Overall, lanadelumab was effective, safe, and well-tolerated in subjects across the lanadelumab clinical program regardless of the baseline HAE attack rate or severity of the disease.

<sup>34</sup> Katelaris, C et al. 2017. Position Paper on Hereditary Angioedema (HAE)  
[https://www.allergy.org.au/images/stories/pospapers/ASCIA\\_HP\\_Position\\_Paper\\_HAE\\_2017.pdf](https://www.allergy.org.au/images/stories/pospapers/ASCIA_HP_Position_Paper_HAE_2017.pdf)

Consistent with the approved indication for Berinert SC, lanadelumab should not be limited only for patients with frequent severe attacks.

The clinical symptom of HAE with normal C1-INH overall resembles that of HAE associated with C1-INH deficiency or dysfunction. For all three sub-types of HAE, unregulated pKal and excess bradykinin generation is generally recognised as the key pathophysiologic defect responsible for the development of HAE attacks. While the pathophysiology of HAE with normal C1-INH remains to be clearly elucidated, angioedema attacks in these patients has been treated with agents targeting the plasma kallikrein-kinin system, suggesting a role for uncontrolled active pKal generation. Based on the mechanism of action of lanadelumab in suppressing pKal generation and bradykinin formation, the preventative treatment effects of lanadelumab could be extrapolated to HAE with normal C1-INH. It is of note that HAE patients with normal C1-INH, which is a very rare form of HAE, do not currently have any approved treatment option in Australia.

The indication for prevention of attacks of HAE without the additional qualifier has been approved by the FDA, Health Canada, and the EMA. Similar to the EU text, a precautionary statement '*There are no available clinical data on the use of Takhzyro in HAE patients with normal C1-INH activity*' will be included in the revised PI. This precautionary statement along with the EU indication wording are considered acceptable by the EMA.

With regard to the phrase '*who are not adequately controlled by on-demand treatments*', the ASCIA position paper states '*any patient experiencing laryngeal attacks must consider this option as should those with severe episodes*'. Similarly, the WAO guidelines state that long term prophylaxis should be considered in all severely symptomatic patients. Shire believes that our proposed indication wording '*for routine prevention of recurrent attacks of HAE*' already encompasses the notion that lanadelumab therapy is indicated for patients who are not adequately controlled by existing on-demand treatments. The proposal of including the additional phrase could potentially limit accessibility of lanadelumab for patients despite the opportunity to fulfil the unmet medical need.

We would also like to comment that the phrase '*who are not adequately controlled by on demand treatments*' does not apply to Berinert SC and the solitary application of the qualifier to lanadelumab could lead to the biased prescribing of Berinert SC over lanadelumab.

In summary, the sponsor proposes to align the indication wording for lanadelumab with that in the EU:

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

### **Proposed dosing recommendation**

Based on the totality of efficacy, pharmacokinetics/pharmacodynamics, and safety data from the pivotal Study DX-2930-03 that consistently demonstrated the greatest treatment effect and optimal benefit-risk profile, Shire proposes the lanadelumab 300 mg every 2 weeks dose regimen as the recommended dose with the potential to reduce the dose frequency to 300 mg every 4 weeks if the patient remains stably attack free on this treatment, especially if the patient has a low body weight. This proposal is in alignment with the EMA-approved wording.

The efficacy analyses showed the lanadelumab 300 mg every 2 weeks dose regimen led to a statistically significant higher reduction (91%) in the number of HAE attacks during the 16 week steady state period (Day 70 to 182) compared with placebo. Moreover, in a post-hoc analysis comparing the active treatment arms, lanadelumab 300 mg every 2 weeks had 62% and 56% greater reduction in HAE attack rate compared to 150 mg every 4 weeks and 300 mg every 4 weeks dose regimens during the steady state period. 77% of subjects treated with 300 mg every 2 weeks dose regimen remained attack free from the

estimated steady state, which is 23% more than 150 mg every 4 weeks dose regimen and 32% more than 300 mg every 4 weeks dose regimen. This information is the key to understand the optimal treatment effect a long term chronic therapy can achieve for patients in real world experience.

Pharmacokinetic/pharmacodynamic analyses showed the lanadelumab 300 mg every 2 weeks dose regimen provided a mean  $C_{min,ss}$  which is 5 fold higher than the  $IC_{50}$  for cHMWK compared to the 300 mg every 4 weeks dose regimen with a  $C_{min,ss}$  which is close to  $IC_{50}$  cHMWK, and the 150 mg every 4 weeks which did not reach the same  $IC_{50}$ . 85% of patients receiving 300 mg every 2 weeks had average concentrations at steady-state ( $C_{ave,ss}$ ) greater than the  $IC_{90}$  of cHMWK, in contrast to only 21% of patients receiving 300 mg every 4 weeks and no subject (0%) receiving 150 mg every 4 weeks.

The pattern of numerical superiority observed for the above mentioned efficacy outcome data and pharmacokinetic/pharmacodynamic parameters with the 300 mg every 2 weeks dose regimen over the other dose regimens remains consistent for patients irrespective of low or high body weight. The overall safety profile demonstrated for the 300 mg every 2 weeks support it as the recommended dose regimen for adolescent and adult patients.

Shire disagrees with drug interruption after 6 months. Although all rollover subjects received one single 300 mg lanadelumab dose at the beginning of Study DX-2930-04, the 'dose and wait' period analysis and results are based on a heterogeneous population consisting of patients with different background levels of disease activity and lanadelumab concentrations varying from 0 to 53,700 ng/mL due to prior treatments in Study DX-2930-03 (26 weeks of either placebo, or lanadelumab 150 mg every 4 weeks, or lanadelumab 300 mg every 4 weeks, or lanadelumab 300 mg every 2 weeks).

The time at which subjects experienced their first attack is correlated with prior lanadelumab exposure levels in Study DX-2903-03: the higher the exposure, the longer a subject remained attack-free, which was observed in the pivotal Study DX-2903-03. Therefore, the clinical significance of the median number of days to first HAE attacks for all rollover subjects is challenging to understand and interpret. This data may lead health care providers or patients to believe that a single dose of lanadelumab provides prolonged protection from angioedema attacks which would be a potentially dangerous assumption not supported by rigorous data.

Lanadelumab has been studied for the prevention of attacks of HAE by evaluating the reduction in attacks in comparison to placebo or reduction in attack rate from the baseline. Pharmacokinetic/pharmacodynamic analyses correlate the maximal efficacy in the 300 mg every 2 weeks dose group with maintaining drug levels above the  $IC_{90}$  for cHMWK, which supports a continual treatment regimen. The data from the dose and wait period analysis provides no permissive guidance to stop dosing, which could result in a life-threatening angioedema attack.

Since each attack is unpredictable and potentially life-threatening, adherence and compliance to a regular lanadelumab treatment is necessary without treatment interruption.

The sponsor understands the need for clinicians to individualise therapy, including an opportunity for flexible dosing. Therefore, extending the dosing interval beyond every 2 weeks to every 4 weeks represents a substantial quality of life benefit for patients if they are well controlled (for example, attack free) on every 2 weeks regimen. This is in line with the dose recommendation approved in the US, Canada and the EU.

In summary, the sponsor proposes to adopt the EU wording as follows, for a simple and clear recommended dosing regimen with the flexibility to individualise therapy based on patient response: The recommended starting dose is 300 mg lanadelumab every 2 weeks.

In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.

**Presentation size**

150 mg/1 mL vial: Similar to the situation in the US, Canada, and the EU, as there is no proposed use for the 150 mg presentation, the sponsor would like to withdraw the 150 mg presentation from the current application.

**Summary and conclusion**

HAE is a long term, serious, severely debilitating and life-threatening condition. The condition also significantly affects the physical, psychological and economic health of the affected patient, and broadly impacts the health of the caregivers and family. In view of the morbidity and disabling nature of the condition of HAE, the limited treatment options, the efficacy and safety data of lanadelumab, the sponsor believes that Takhzyro will have an important position in clinical treatment of patients with HAE.

The use of Takhzyro for prevention of HAE attacks has been recognised by three comparable overseas regulators: the FDA, Health Canada, and the EMA. Based on our reading of the Delegate's Overview, the Delegate is not objecting to alignment of the indication and dosage wording with the EU text and is seeking an endorsement by the ACM on these recommendations.

We believe the benefit/risk profile of Takhzyro represents a marked improvement over existing therapies:

- Lanadelumab demonstrated highly statistically significant and clinically meaningful reductions in HAE attacks over the 26 week treatment period compared to placebo across primary and all secondary efficacy analyses. Results were consistent regardless of run-in period attack rate or history of laryngeal attacks.
- Lanadelumab treatment resulted in a high proportion (77%) of subjects being attack-free once steady state is achieved.
- Lanadelumab is a fully human, recombinant, monoclonal antibody, devoid of the safety concerns associated with plasma derived C1-INHs (for example, transmission of infectious pathogens, infusion related reactions, venous thromboembolic events). No dose-limiting toxicities or contraindicated populations have been identified to date for the proposed use of lanadelumab.
- Lanadelumab will be provided as a ready-to-use 300 mg/2 mL formulation for subcutaneous injection. The convenience of less frequent administration (once or twice monthly) improves patient care in comparison to existing therapies. Self-administration is thought to support patient compliance, patient knowledge, and patient independence.

In conclusion, the sponsor supports the recommendation to approve registration of Takhzyro with the following indication and dosing recommendation:

Indication:

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

**Dosing recommendation:** The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.

### Advisory Committee Considerations<sup>35</sup>

The ACM taking into account the submitted evidence of efficacy, safety and quality, considered Takhzyro, a subcutaneous injection of lanadelumab after reconstitution with the supplied water for injections, to have an overall positive benefit-risk profile for the revised indication:

*Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (C1-esterase inhibitor deficiency or dysfunction) in patients aged 12 years and older.*

rather than the indication presented to the committee which was:

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

In providing this advice the ACM noted that:

- No subjects with HAE and normal C1-INH were included in the product trials.
- HAE with normal C1-INH is not the same disease as HAE with deficient (type I) or dysfunctional (type II) C1-INH which were included in the product trials.
- The optimal dosing regimen for different weight groups are unable to be determined from the currently available data, in view of the small numbers of subjects studied to date.
- The optimal dosing regimen for longer term prophylactic management has not been established due to data limitations.
- The application for the 150 mg dose presentation has been withdrawn by the sponsor but will likely be needed for appropriate dosing of most 12 year old children and many other patients.
- The product safety study was conducted in paediatric patients aged over 12 years and these were overall small in number (n = 23).
- The EMA's CMPH issued a positive opinion for lanadelumab and supported the following indication:

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

The ACM also:

- advised that the sponsor should consider including studies on longer term prophylactic management as part of the post-approval studies.
- expressed concern that the 150 mg dosing option was not available, as there was no evidence to suggest that this dose should not be made available and suggested that future studies examine this dosing option.

<sup>35</sup> The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- advised that the sponsor should be requested to provide further information regarding optimal dosing in different weight groups, especially with respect to having a larger number of patients in the larger weight groups.

### ***Specific advice***

The ACM advised the following in response to the delegate's specific questions on the submission:

- 1. What is the advice of the committee with regards to the wording of the indications? Does the ACM consider that the indications should specify HAE patients with C1-INH deficiency or dysfunction who have frequent severe attacks and who are inadequately controlled by on-demand treatments?***

The ACM considered that the indication should specify for HAE patients with C1-INH deficiency or dysfunction, as HAE patients with normal C1-INH were not included in the studies.

The ACM advised that attack severity can vary, and the term 'severe' would need to be defined to be considered useful. Additionally, some patients in the least frequent attack stratum studied in Study DX-2930-03 (main efficacy study) benefited from 300 mg every 2 or 4 weeks. Therefore, the ACM agreed that the indication should contain the wording 'recurrent attacks' as consistent with the EU supported indication.

- 2. What is the committee's advice with regards to the appropriate dosing recommendations?***

The ACM noted that the pivotal trial was not set up to compare the efficacy of the three doses regimens studied (150 mg every 4 weeks; 300 mg every 4 weeks; and 300 mg every 2 weeks) but all three doses studied were effective.

The ACM agreed with the recently supported dose recommendation in the EU:

*The recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.*

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

## **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Takhzyro lanadelumab 300 mg in 2 mL solution for injection in a 5 mL vial indicated for:

*Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (C1-esterase inhibitor deficiency or dysfunction) in patients aged 12 years and older.*

### **Specific conditions of registration applying to these goods**

- Batch release testing and compliance with Certified Product Details (CPD)
  - It is a condition of registration that all batches of Takhzyro imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - It is a condition of registration that each batch of Takhzyro imported into/manufactured in Australia is not released for sale until samples and/or the

manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index>.

- c. The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact [Biochemistry.Testing@health.gov.au](mailto:Biochemistry.Testing@health.gov.au) for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at <https://www.tga.gov.au/publication/testing-biological-medicines>

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

2. Takhzyro (lanadelumab) is to be included in the Black Triangle Scheme. The PI and CMI for Takhzyro must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
3. The lanadelumab EU-Risk Management Plan (RMP) (version 1.5, dated 16 October 2018, data lock point 1 September 2017), with Australian Specific Annex (version 1.2, dated 10 January 2019), included with submission PM-2018-01464-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

<https://www.tga.gov.au>