

**5.06 LANADELUMAB,
Solution for injection 300 mg in 2 mL,
Takhzyro[®],
Shire Australia Pty Ltd**

1 Purpose of Application

- 1.1 The submission requested a Section 85, Authority Required listing for lanadelumab as routine prophylaxis of recurrent attacks of hereditary angioedema (HAE). Lanadelumab has not previously been considered by the Pharmaceutical Benefits Advisory Committee (PBAC) for this indication.
- 1.2 The requested listing was based on a cost-minimisation analysis (CMA) of lanadelumab compared with intravenous (IV) C1-esterase inhibitor (C1-INH) in patients with HAE.

Registration and subsidisation of IV C1-INH for HAE in Australia

- 1.3 IV C1-INH concentrate for the management of HAE was considered by the Medical Services Advisory Committee (MSAC) in July 2015 (application number 1394). The MSAC assessment considered the use of IV C1-INH for three indications: treatment of acute attacks of HAE, pre-procedural prophylaxis, and routine (long-term) prophylaxis. Two plasma derived forms of IV C1-INH concentrate (Cinryze and Berinert), with different pharmacokinetics / pharmacodynamics (PK/PD), were evaluated for the treatment of acute attacks, but only Cinryze was evaluated for pre-procedural and routine prophylaxis, as IV Berinert is not Therapeutic Goods Administration (TGA)-approved for these indications.
- 1.4 The MSAC advised that routine prophylaxis with IV C1-INH was only justified in terms of cost-effectiveness beyond a pre-prophylaxis rate of 8 acute attacks per month, and noted that, consistent with TGA approvals, this advice only applied to the Cinryze product (Application No. 1394, PSD, July 2015 MSAC Meeting).¹
- 1.5 As a result of the National Blood Authority (NBA) tender process, IV Berinert is the formulation of IV C1-INH that is subsidised in Australia for the three indications.
- 1.6 As outlined above, three plasma-derived C1-INH products were discussed in the submission: the two products for IV administration (IV Berinert and IV Cinryze), and one product for subcutaneous (SC) administration (Berinert SC):
- IV Cinryze is TGA indicated for treatment of acute HAE attacks and for use as routine prophylaxis, and was the formulation on which the MSAC based its cost-

¹ <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1394-public>

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effectiveness analysis for the use of IV C1-INH for routine prophylaxis. However, this formulation is not currently accessible through, or funded by, the NBA in Australia;

- IV Berinert is TGA indicated for treatment of acute HAE attacks only (not for prophylaxis). It is accessed and funded through the NBA for routine prophylaxis.
- Berinert SC has recently been approved by the TGA. It is given for routine prophylaxis (it is not indicated for treatment of acute attacks) and is not currently publicly funded in Australia.

The ESC considered that the pharmacokinetics and pharmacodynamics of IV Berinert and IV Cinryze differ, and the equi-effective doses of the two formulations of IV C1-INH, when used for routine prophylaxis, have not been established.

- 1.7 The key components of the clinical issues addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with HAE treated with on-demand treatment 12 or more times within a 6-month period, despite receiving a maximum tolerated dose of danazol (unless clinically inappropriate) as routine prophylaxis for HAE. The requested restriction also included patients who have experienced a life-threatening HAE attack within the previous 12 months despite receiving the maximum tolerated dose of danazol (unless danazol is clinically inappropriate).
Intervention	Lanadelumab subcutaneous injection.
Comparator	Intravenous C1-INH (Berinert®), currently available for routine prophylaxis in HAE on the National Blood Authority National Product Price List, under the National Blood Agreement.
Outcomes	HAE attack rate HAE attack rate requiring acute treatment Percentage responder
Clinical claim	Non-inferiority vs intravenous C1-INH and standard of care.

C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema
Source: Table 1, p7, and Section 2.8.2, p148 of the submission.

2 Requested listing

- 2.1 The restriction requested in the submission is outlined below.

Name, restriction, manner of administration, form	Max. Qty (vial)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
LANADELUMAB 300 mg/2 mL, Solution for subcutaneous injection, vial	1-2	5	\$ [REDACTED] for one vial	Takhzyro® Shire Australia Pty Ltd
Category/Program:	General – General Schedule (S85) (Code GE)			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Hereditary Angioedema (HAE)			
PBS Indication:	Hereditary Angioedema in patients for whom the use of danazol is not clinically appropriate or not effective			
Treatment phase:	Initial			
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing			
Treatment criteria:	Must be treated by a specialist immunologist or allergist.			

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Clinical criteria:	<p>Patient must have a confirmed and documented diagnosis of hereditary C1-inhibitor deficiency or dysfunction,</p> <p>AND</p> <p>Patient must</p> <ul style="list-style-type: none"> • be currently receiving C1-inhibitor as routine prophylaxis for HAE; OR • within the previous 12 months, have experienced a life-threatening HAE attack, despite receiving a maximum tolerated dose of danazol (unless clinically inappropriate); OR • have experienced 12 or more treated HAE attacks within the prior 6 months, despite receiving a maximum tolerated dose of danazol (unless clinically inappropriate) as routine prophylaxis for HAE; <p>AND</p> <p>Patient must not receive more than 6 months of treatment under this restriction.</p>
Population criteria:	Patient must be aged at least 12 years.
Prescriber Instructions:	<p>The name of the specialist consulted must be provided at the time of application for initial supply.</p> <p>History of HAE attacks should be based on documented use of acute treatment prescribed by a physician.</p> <p>ASCIA endorses the use of validated tools for assessment of frequency and severity of attacks which may aid the clinician in the decision to prescribe long-term prophylaxis.</p> <p>The authority application must be made in writing and must include:</p> <p>a) a completed authority prescription form; and</p> <p>i) details of prior danazol therapy used as routine prophylaxis (dosage, date of commencement and duration of therapy) unless clinically inappropriate; and</p> <p>ii) details of treated HAE attack/s (date of attack and treatment used) experienced over the baseline period; and</p> <p>iii) (if appropriate) acknowledgement signed by a parent or authorised guardian.</p>

Category/Program:	General – General Schedule (S85) (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Hereditary Angioedema (HAE)
PBS Indication:	Hereditary Angioedema in patients for whom the use of danazol is not clinically appropriate or not effective
Treatment phase:	Continuing
Restriction:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	Must be treated by a specialist immunologist or allergist or general physician experienced in the management of HAE.

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Clinical criteria:	<p>Patients must have previously received PBS-subsidised initial treatment with this drug for this condition,</p> <p>AND</p> <p>Patient who qualified based on attack frequency must have demonstrated an adequate response to PBS-subsidised treatment with this drug,</p> <p>AND</p> <p>Patient must not receive more than 6 months of treatment under this restriction without undergoing a review and documented reassessment by the prescribing physician to determine whether treatment is still warranted or required.</p>
Population criteria:	Patient must be aged at least 12 years.
Definitions	<p>An adequate response to lanadelumab is defined as follows:</p> <p>Patient must have achieved at least a 50% reduction of the baseline treated attack rate, based on a time adjusted assessment over the treatment course (minimum treatment period of 3 months).</p> <p>The first assessment should, where possible, be completed by the same physician who initiated treatment with lanadelumab.</p> <p>A patient who fails to respond to a course of PBS-subsidised lanadelumab as routine prophylaxis for HAE will not be eligible to receive further PBS-subsidised treatment with lanadelumab for this condition within 6 months of the date on which treatment was ceased.</p>
Note:	In patients who are attack free on treatment, a dose reduction to 300 mg lanadelumab every 4 weeks may be considered.

- 2.2 The TGA recommended starting dose is 300 mg lanadelumab every 2 weeks; in patients who are “stably attack free” on treatment, a dose reduction to 300 mg lanadelumab every 4 weeks may be considered. A maximum quantity of 2 vials, with 5 repeats, would be required to provide 6 months of initial therapy. Given the unpredictable nature of acute HAE attacks, this duration of therapy is likely to be required to adequately determine whether a patient is “stably attack free” on treatment, and whether a dose reduction to 300 mg every four weeks should be considered. For continuing therapy, a maximum quantity of 2 vials with 5 repeats would also be necessary in order to provide 6 months of therapy for those patients who continue on the higher dose. The dispensed price for maximum quantity (DPMQ) in the requested listing is for a maximum quantity of one vial. The DPMQ for a maximum quantity of two vials would be \$ [REDACTED].
- 2.3 The submission did not propose a special pricing arrangement.
- 2.4 The patient population defined by the submission’s proposed restriction criteria differed from both the eligible population for the nominated main comparator, IV C1-INH, as listed in the NBA’s National Product Price List, and the trial population in the key lanadelumab trial (the HELP trial).
- The requested restriction (in the submission) was for patients who experience 12 attacks over a 6 month period while receiving danazol, while NBA-funded IV C1-INH (for routine prophylaxis) is restricted to patients who experience the

equivalent of eight or more acute attacks per month. The MSAC advised that use of IV C1-INH as routine prophylaxis was only justified in terms of cost-effectiveness in this targeted population (Application No. 1394, PSD, July 2015 MSAC Meeting)². Furthermore, the eligibility criteria in the HELP trial only required patients to have a baseline rate of at least one HAE attack per 4 weeks, with the majority of patients required to discontinue any routine prophylaxis prior to assessment.

- Patients are not eligible for routine prophylaxis with NBA-funded IV C1-INH on the basis of experiencing a single life-threatening HAE attack while receiving oral prophylaxis, nor were patients eligible for enrolment in the HELP trial on this basis. The ESC noted that no data were provided to support listing in this patient population.
- 2.5 The PSCR (p1) restated that the intent of the proposed restriction is to “reflect the patients currently accessing NBA funded IV C1-INH as prophylaxis”.
- 2.6 The PSCR (p1) outlined how the target population for the PBS restriction, as proposed in the submission, was derived:
- The DUSC ‘Icatibant: 24 month predicted versus actual analysis’ (June 2015) showed that 13.8% of patients received more than 12 doses of icatibant in 2012-13. (Icatibant is PBS-subsidised for the emergency treatment of acute attacks of HAE, the DUSC analysis is discussed further in Paragraph 6.64 below);
 - A survey of Australian specialists found that 14.5% (18 of 124) of their patients with HAE received IV C1-INH as routine prophylaxis³;
 - The submission appeared to assume that the 14.5% of patients receiving IV C1-INH as prophylaxis in the survey corresponds with the 13.8% of patients in the DUSC analysis receiving 12 or more doses of icatibant per year. The submission considered that the DUSC analysis may underestimate the extent of use of icatibant in current practice and thus increased the threshold from the equivalent of one treated attacks per month to two.
- 2.7 The PSCR (pp. 1-2) claimed that the proposed criteria in the submission were “more rigorously defined, objective”, and that “the potential for broad use of routine prophylaxis is greater with the NBA indication than it is for the proposed PBS listing for lanadelumab”.
- 2.8 The PSCR stated that an alternative option was for the PBAC to consider listing lanadelumab with the same wording as the NBA access criteria, i.e. ‘second line, as routine (long-term) prophylaxis for patients who experience the equivalent of eight or more acute attacks per month’.

² <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1394-public>

³ Poster presentation of Katelaris CH, Perram F, et al. Hereditary angioedema attack prophylaxis management in Australian patients. *Internal Medicine Journal*. 2017; 47 (Suppl. 5):27.

- 2.9 The ESC noted that use in patients who experience fewer attacks than specified in the NBA criteria would be outside the population in which MSAC advised that IV C1-INH would be cost-effective. As such, the ESC considered that listing on a cost-minimisation basis would only be appropriate if the clinical criteria for initial treatment with lanadelumab were the same as the NBA indication for routine prophylaxis, i.e. that eligibility should be restricted to second-line use in patients who experience the equivalent of eight or more acute attacks per month. However, the PBAC advised that the clinical role of lanadelumab is broader than the population in whom C1-INH was considered cost-effective by MSAC (as outlined in Section 7).
- 2.10 The submission proposed that treated attacks be used as the basis upon which access to lanadelumab is determined, as the use of on-demand treatment provides both a measure of disease severity and of response after initiation of routine prophylaxis. However, the ESC noted that the NBA criteria did not specify that the acute attacks had to be treated. Further, the PBS listing for icatibant for anticipated emergency treatment of acute HAE attacks does not specify either the site or the severity of the attack to be treated. While icatibant is only intended to be used for treatment of laryngeal and moderate-severe abdominal attacks, the PBAC previously considered that there would be a high risk that patients would use icatibant where symptoms are milder than in the intended population, i.e. for cutaneous and mild abdominal attacks (Icatibant Public Summary Document (PSD), July 2011 PBAC Meeting). Therefore, there is no way of confirming either the location or the severity of the attack for which icatibant was administered if the patient did not subsequently seek medical attention.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Lanadelumab 300 mg/2 mL solution for injection was granted orphan drug designation by the TGA on 21 February 2018, and was listed on the Australian Register of Therapeutic Goods (ARTG) on 30 January 2019 for the following indication:
- Lanadelumab is indicated for the routine prevention of recurrent attacks of HAE (C1-esterase-inhibitor deficiency or dysfunction) in patients aged 12 years and older.
- 3.2 The TGA evaluator considered that neither the optimal dose nor the optimal dosing frequency had been determined and noted the lack of long-term data.

Previous PBAC consideration

- 3.3 This is the first submission of lanadelumab for PBAC consideration.

4 Population and disease

- 4.1 HAE is a rare, autosomal dominant, potentially severely debilitating, and life-threatening condition that manifests as painful, unpredictable, intermittent attacks of subcutaneous or submucosal oedema of the face, upper airways, gastrointestinal tract, limbs and/or genitalia. Attacks recur with unpredictable frequency, intensity and duration, placing a burden on the daily life of patients.
- 4.2 There are three types of HAE. Types 1 and 2 are caused by mutations in the C1-INH gene. Type 1 is due to deficiency of C1-INH, and type 2 is due to dysfunction of C1-INH. Type 3 is characterised by normal C1-INH functional levels. The key trial of lanadelumab (the HELP trial) enrolled patients with Type 1 or 2 HAE.
- 4.3 Lanadelumab is a human, monoclonal antibody (IgG1/k-light chain) that inhibits plasma kallikrein with a half-life of 14 days.
- 4.4 Attack frequency and severity among patients is variable, with most patients experiencing few attacks, which can be managed with on-demand therapy, such as with icatibant (PBS-subsidised for emergency treatment of acute HAE attacks, available as a SC injection) or Berinert (available through the NBA as an IV injection). Other patients have multiple attacks per month or per week, necessitating prophylactic treatment. Oral prophylactic therapies include danazol and tranexamic acid. Where oral therapies are ineffective or clinically inappropriate, patients who experience the equivalent of eight or more attacks per month can access IV C1-INH (Berinert) as routine prophylaxis. IV C1-INH concentrate, derived from human plasma, is available on the NBA's National Product Price List and can be self-administered in the home setting with a twice weekly dosing frequency.

5 Comparator

- 5.1 The submission nominated IV C1-INH as the main comparator.
- 5.2 The evaluation and ESC considered that the nominated comparator, IV C1-INH, would only be the appropriate comparator if use is limited to patients who meet the NBA indication for routine prophylaxis with IV C1-INH. The evaluation and ESC considered that the appropriate comparator in all other patients would be standard of care (on-demand treatment plus oral routine prophylaxis).
- 5.3 The ESC noted that the submission, reinforced by the PSCR, had proposed that the PBS restriction for lanadelumab be the same as the NBA indication for IV C1-INH for routine prophylaxis (second-line use in patients who experience the equivalent of eight or more acute attacks per month). As such, the ESC considered that IV C1-INH was the appropriate comparator if use were to be limited to this population.
- 5.4 The clinical trial of lanadelumab (HELP trial) included patients with a baseline rate of at least one HAE attack per 4 weeks, and the mean baseline rate was 3.2 to 4.0 attacks per 4 weeks. As such, the ESC considered that use in a broader population than

outlined in the NBA criteria for IV C1-INH may be clinically appropriate, but would need to be informed by a cost-utility analysis versus standard care.

- 5.5 In some sections of the submission, IV Berinert was specifically nominated as the main comparator, and the economic and financial analyses were based on the dosage and price of IV Berinert. While IV Berinert is the formulation of C1-INH used in Australian clinical practice, it is not TGA registered for this indication and its cost-effectiveness as routine prophylaxis was not evaluated by MSAC, hence the submission did not present any clinical data for this preparation.
- 5.6 The MSAC's assessment of the efficacy and cost-effectiveness of IV C1-INH for routine prophylaxis was based on the Cinryze formulation. The ESC considered that, for the population defined by MSAC, the cost per patient for lanadelumab should be no more than the cost per patient at which IV Cinryze was considered cost-effective by MSAC including any price reductions realised through the NBA tendering arrangements.
- 5.7 Berinert SC was recently listed on the ARTG for prevention of recurrent HAE. The submission nominated SC C1-INH as a potential near-market comparator. The cost-effectiveness of SC C1-INH has not been assessed by the MSAC, and the submission did not present an evaluation of the cost-effectiveness of lanadelumab compared with SC C1-INH.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The hearing outlined the patient perspective of HAE and the significant impact that acute attacks have on patient quality of life, including that the pain and swelling can prevent patients from participating in their usual daily activities such as travel or attending school, work or social events. The attacks can be unpredictable, sudden and severe with the potential for attacks to be life-threatening. The current therapy (IV C1-INH) is effective at preventing attacks, and can help patients return to normal functional activities. However, it is associated with significant administration difficulties as it is given intravenously twice per week.
- 6.2 The presenter at the hearing outlined that a broader listing for lanadelumab (than is currently in place for IV C1-INH) would be beneficial as there are patients without access to effective prophylactic treatment because they don't meet the NBA criteria. Danazol is less effective and is associated with adverse events that can significantly impact patient quality of life such as weight gain, voice changes and hair growth.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (20), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments highlighted the significant morbidity associated with HAE such as pain and swelling and the anxiety associated with the potential for future attacks. In particular, the comments highlighted the difficulties of administering the currently available prophylactic therapy, which requires IV administration. The comments discussed the risk of infection and venous damage, the need for central access in some patients, the time associated with IV administration and logistical issues. The comments outlined that some patients (who are eligible) cannot take IV C1-INH due to these difficulties. Overall, consumers considered there would be considerable benefits, in terms of administration, to having an effective prophylactic therapy available that can be administered SC.
- 6.4 The consumer comments also outlined that there are some patients who are ineligible for IV C1-INH under the NBA criteria, but whose quality of life would improve with access to an effective prophylactic therapy.

Clinical trials

- 6.5 The submission presented what it described as an “informal indirect comparison”, in which the results from single arms from the trials were compared side-by-side, without performing any statistical analyses. The submission was based on one randomised trial comparing lanadelumab with placebo (HELP trial), one randomised crossover trial comparing IV C1-INH (Cinryze) with placebo (CHANGE-B trial), and one randomised crossover trial comparing SC C1-INH (Berinert SC) with placebo (COMPACT trial). No trials of IV C1-INH (Berinert IV) were presented.
- HELP trial was a multicentre, randomised, double-blind, placebo controlled trial, comparing three dose regimens of lanadelumab with placebo as routine prophylaxis for acute attacks in patients with C1-INH deficiency (type I) or C1-INH dysfunction (type II) HAE. There were four treatment arms:
 - Lanadelumab 300 mg SC every 2 weeks (q2wks) (N=27),
 - Lanadelumab 300 mg SC every 4 weeks (q4wks) (N=29),
 - Lanadelumab 150 mg SC q4wks (N=28) (not requested for listing),
 - Placebo SC q2wks (N=41)
 - COMPACT trial was a multicentre, randomised, double blind, placebo controlled, incomplete-crossover trial of SC C1-INH (Berinert SC) as routine prophylaxis for acute attacks in patients with type I or II HAE. Patients were randomly assigned in a 1:1:1:1 ratio to the following treatment arms: 40 IU/kg body weight SC C1-INH twice weekly in the first 16 week treatment period followed by placebo in the second 16 week treatment period (N=23), or vice versa (N=22); or 60 IU/kg body

weight SC C1-INH twice weekly for in the first treatment period followed by placebo in the second treatment period (N=22), or vice versa (N=23). However, this was not consistent with the formulation and dose of Berinert used in the economic and financial analyses, which were based on the IV formulation dosed at 20 IU/kg body weight twice weekly.

- CHANGE-B was a multicentre, randomised, double-blind crossover trial comparing IV C1-INH (Cinryze) with placebo for routine prophylaxis of HAE attacks in patients with type I or II HAE⁴. Patients with at least 2 attacks per month were randomised in a 1:1 ratio to receive:
 - IV C1-INH 1,000 IU every 3 to 4 days for 12 weeks, followed by placebo every 3 to 4 days for 12 weeks (N=11), or
 - Placebo every 3 to 4 days for 12 weeks, followed by IV C1-INH 1,000 IU every 3 to 4 days for 12 weeks (N=11).

CHANGE B was the key trial on which the MSAC based its consideration of the effectiveness of IV C1-INH for routine prophylaxis of HAE attacks, although the health outcomes used in the economic evaluation of IV C1-INH were sourced from a single-arm study of IV C1-INH administered at a dose of 1,000 IU every 3 to 7 days⁵.

- 6.6 The submission stated that, given the lesser quality and uncertain applicability of the data from CHANGE-B, the outcomes for SC C1-INH from the COMPACT trial were used as a proxy for outcomes for IV C1-INH prophylaxis. A claim of non-inferiority was made on the outcomes of HAE attack rate during the treatment period, and use of rescue medication during the treatment period.
- 6.7 Details of the trials presented in the submission are provided in the table below.

⁴ While the inclusion did not specify that patients must have type I or type II HAE, patients were required to have low C1-INH antigenic level (*type I*) or low C1-INH functional level (*type II*), or a known HAE-causing C1-INH mutation.

⁵ Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Med.* 2012; 125 (9):938 e1-7.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
HELP	Clinical Study Report: HELP Study®: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE).	September 2017
	Hereditary Angioedema (HAE) – Assessment of Patient Reported Outcome Data from the DX-2930- 03 HELP Study®– Primary Objectives. Banerji A, Riedl M, Berstein JA, et al. Effect of lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks.	August 2017 JAMA 2018; 320(20): 2108-2121.
COMPACT	Longhurst H, Cicardi M, Craig T et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor.	NEJM 2017; 376(12): 1131-40.
	Lumry WR, Craig T, Zuraw B, et al. Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema.	J Allergy Clin Immunol Pract 2018; 6(5): 1733-41 e3.
CHANGE-B	Clinical Study Report: LEVP 2005-1/Part B CHANGE Trial (C1-Inhibitor in Hereditary Angioedema Nanofiltration Generation evaluating Efficacy): A Double-blind, Placebo-controlled, Clinical Study to Investigate the Efficacy and Safety of C1INH-nf (Cinryze™), Purified C1 Esterase Inhibitor (Human) for the Prevention of Hereditary Angioedema (HAE) Attacks. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema.	October 2007 NEJM 2010; 363(6): 513-22.

C1-INH= C1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous; SC = subcutaneous
Source: Table 13, pp35-36 of the submission.

6.8 The key features of the evidence included in the indirect comparison are summarised in the table below.

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Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	
Lanadelumab trial						
HELP	300 mg lanadelumab SC every 2 weeks ^a	27	R, DB 26 weeks	Low	≥ 1 attack / month (investigator-confirmed attacks) No restriction on line of therapy	Number of investigator-confirmed HAE attacks during the treatment period and number of attacks requiring acute treatment
	300 mg lanadelumab SC every 4 weeks ^a	29				
	150 mg lanadelumab SC every 4 weeks ^a	28				
	PBO SC every 2 weeks ^a	41				
C1-INH trials						
SC Berinert						
COMPACT	C1-INH 60 IU/kg (0.12 mL/kg) SC twice weekly ^b xo PBO twice weekly	22	R, DB, XO 16 weeks for each treatment period	Low	≥ 2 attacks / month (attacks requiring acute treatment, medical attention or causing significant functional impairment) No restriction on line of therapy	The number of investigator-confirmed HAE attacks during the treatment period and number of uses of rescue medication
	PBO twice weekly xo C1-INH 60 IU/kg (0.12 mL/kg) SC twice weekly ^b	23				
	C1-INH 40 IU/kg (0.08 mL/kg) SC twice weekly ^b xo PBO twice weekly	23				
	PBO twice weekly xo C1-INH 40 IU/kg (0.08 mL/kg) SC twice weekly ^b	22				
IV Cinryze						
CHANGE-B	C1-INH 1,000 IU (10 mL) IV twice weekly xo PBO twice weekly	11	R, DB, XO 12 weeks on each treatment period	Lodsw	≥ 2 attacks / month No restriction on line of therapy	The number of patient reported HAE attacks during the treatment period and number of open-label rescue infusions of IV C1-INH
	PBO twice weekly xo C1-INH 1,000 IU (10 mL) IV twice weekly	11				
Indirect comparison: Lanadelumab vs C1-INH – High risk of bias						

C1-INH = C1-esterase inhibitor; DB = double blind; HAE = hereditary angioedema; IU = international units; IV = intravenous; PBO = placebo; R = randomised; SC = subcutaneous; XO = cross over trial.

^a To maintain blinding, placebo doses were administered in between doses of lanadelumab for subjects randomised to lanadelumab 150 mg or 300 mg 4 weekly. Also for each 300 mg dose of lanadelumab, each subject received a total of 2 mL divided into 2 separate 1.0 mL injections. For each 150 mg dose of lanadelumab, each subject received a 1.0 mL injection of lanadelumab and a 1.0 mL injection of placebo. For each placebo dose, each subject received a total of 2 mL, divided into 2 separate injections on placebo.

^b Actual dose rounded to nearest 500 IU or 1 mL.

Source: Compiled during the evaluation based on information provided in Sections 2.3-2.4 of the submission.

6.9 The submission stated that no formal quantitative indirect comparison of lanadelumab versus IV C1-INH or SC C1-INH was undertaken because differences in the designs of the included trials, the included populations, and the approaches to the analysis of the key outcomes, were likely to limit the exchangeability of outcomes. These major transitivity issues cast doubt on the validity of any indirect comparison, regardless of whether it is quantitative or qualitative. Therefore, the ESC and PBAC

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considered that the indirect comparison presented in the submission was subject to a high risk of bias.

6.10 The key differences across the trials that may cause treatment effect heterogeneity are summarised in the table below.

Table 4: Differences across the trials which may cause treatment effect heterogeneity

	HELP Lanadelumab vs placebo	COMPACT SC C1-INH vs placebo	CHANGE-B IV C1-INH vs placebo
Study design	Parallel group	Crossover	Crossover
Treatment duration	26 weeks	16 weeks	12 weeks
Patient populations			
Age For inclusion Mean (SD)	≥12 years 40.7 (14.7) years	≥12 years 39.6 (14.9) years	≥6 years 38.5 (16.6) years
Baseline attack rate For inclusion in randomised treatment period	≥1 attack per four weeks during run-in	≥ 2 attacks per four weeks during run-in	≥ 2 attacks per month at baseline
Approach to assessment for eligibility	≥1 attack during the first 4 weeks or ≥2 attacks during the second 4-weeks of an up to 8-week run-in	≥1 attack during the first 2 weeks or 2 attacks during any 4-week period of the 8- week run-in	Not described
Severity of qualifying attack	Any	Attacks requiring acute treatment, medical attention or causing significant functional impairment)	Any
Mean attacks/4 weeks	3.2 to 4.0 (mean in 'last month' at baseline was 3.9, SD 4.2)	4.0 to 4.6	Not reported
Attack rates during treatment with placebo	Mean: 2.0 (95% CI: 1.6, 2.4); Median: 1.7 Maximum: 8.3 ^d	Mean: 3.6 & 4.0; Median: 4.0 & 3.8	Mean: 4.2; Median 4.5
Concomitant HAE therapy			
LTP permitted during treatment period			
Oral	No	Yes –if receiving a stable dose 1 of the 90 patients continued to receive oral LTP during trial	Yes – if receiving a stable dose 3 of the 22 patients continued to receive oral LTP during trial
Rescue medication for acute HAE attacks			
Limitations of use	Patients permitted use at any time	Patients permitted use at any time	If the investigator determined it was in the patient's best interest
Medications allowed	Investigator's usual care. Included icatibant, IV C1- INH, ecallantide and conestat alfa ^a	Icatibant, IV C1-INH, ecallantide and fresh-frozen plasma ^a	IV C1-INH only
Outcome measures and statistical methods			
Number of attacks	Only investigator-confirmed attacks included in the analysis	Only investigator-confirmed attacks included in the analysis	All patient-reported attacks included in the analysis

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	HELP Lanadelumab vs placebo	COMPACT SC C1-INH vs placebo	CHANGE-B IV C1-INH vs placebo
Use of rescue medication	Number of investigator-confirmed attacks requiring acute treatment	Number of uses of rescue medication ^c	Number of rescue infusions of C1-INH Double infusions counted as 2 infusions.
	Use of rescue medication reported by the patient Only use for investigator-confirmed attacks were included in the analysis. ^b	Patient reported. Requirement for rescue medication did not have to be confirmed by the investigator.	Requirement for rescue medication determined by the investigator.
Statistical methods	Between group comparison with placebo	Within subject comparison with placebo	Within subject comparison with placebo

C1-INH = C-1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous; LTP = long-term (routine) prophylaxis; SC = subcutaneous; SD = standard deviation.

^a Ecallantide is a kallikrein inhibitor, and is registered in the US for on-demand treatment of HAE attacks. Current international clinical guidelines for the management of HAE recommend both ecallantide and icatibant for on-demand treatment of acute HAE attacks, and do not indicate any preference for one drug over the other.⁶ Only 2.4% of patients in HELP trial received conestat alfa, which is a human recombinant C1-INH.

^b It was not clear whether the investigator confirmed that the attack was of a severity requiring rescue medication, or if all use of rescue medication for investigator-confirmed attacks was included.

^c It was not clear whether patients could receive more than one rescue medication for the same attack and, if so, whether this was counted in the number of uses of rescue medication (i.e. whether this was the number of attacks for which patients used rescue medication or the actual number of doses of rescue medication received by the patient).

^d This was the 'Treatment period HAE attack rate (attacks/month)' Source: Table 14.2.2.1 of the HELP CSR

Source: Table 43, p 116, Table 16, pp53-4, Table 19, p62 and Table 21, p66 of the submission; Tables 14.1.4.2, p230; 14.1.6.3, p306 HELP CSR; Longhurst et al (2017); Section 4.7.2.2, p38 COMPACT Protocol version 2.

6.11 There were considerable differences between the three trials in terms of the minimum average attack rate required for eligibility for enrolment, with HELP only requiring an average of one attack (of any severity) per 4 weeks, while both C1-INH trials required an average baseline attack rate of 2 attacks per month, with COMPACT further requiring that the attacks must be of a severity requiring acute treatment, medical attention or causing significant functional impairment. The mean number of attacks per month at baseline was 3.2 to 4.0 in HELP and 4.0 to 4.6 in COMPACT (not reported for CHANGE-B). The PBAC noted that in the placebo arm of the HELP trial, the median attack rate during the treatment period was 1.7 attacks per month, with a maximum of 8.3 attacks per month.

6.12 The primary outcome in all three trials was the number of HAE attacks, regardless of the location or severity of the attacks. All three trials also reported the use of rescue treatment for HAE attacks as an efficacy outcome. The evaluation considered that the most clinically relevant outcome was prevention of laryngeal and severe abdominal attacks, which was likely to be reflected in the extent of use of on-demand treatment.

⁶ Maurer M, Magerl M, *et al.* The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *World Allergy Organization Journal.* 2018; 11 (1):5.
Zuraw BL, Banerji A, *et al.* US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract.* 2013; 1 (5):458-67.

However, reporting of the use of rescue medication varied across the trials, which limited the comparability of this outcome.

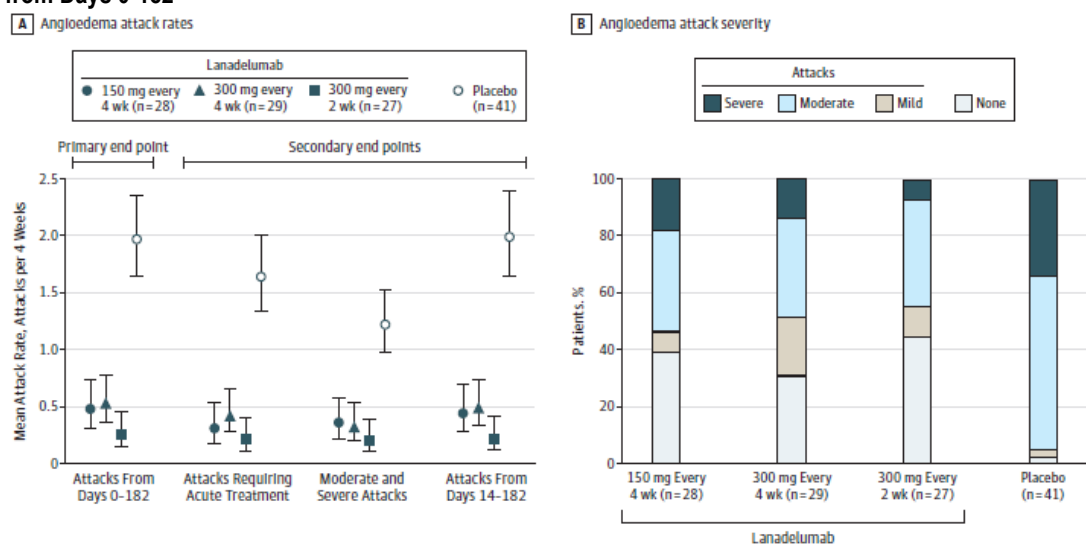
- 6.13 The submission did not nominate a non-inferiority margin for the indirect comparison of lanadelumab and C1-INH as routine prophylaxis for prevention of acute HAE attacks.
- 6.14 The criteria for eligibility regarding baseline attack rates in the trials were not consistent with either the proposed PBS clinical criteria for initial treatment with lanadelumab, or the indication for IV C1-INH funded by the NBA. Similarly, in contrast to the requested restriction for lanadelumab, patients in all three trials were not required to be receiving routine oral prophylaxis over the period when the qualifying minimum HAE attack rate was determined. The PBAC also noted that only 5.6% of patients in the HELP trial had received prior danazol, while the proposed PBS restriction required patients to have previously been treated with danazol (unless clinically inappropriate).
- 6.15 It was not possible to determine the proportion of patients in each trial who would have met the proposed restriction criteria for lanadelumab, or the NBA indication for access to IV C1-INH as routine prophylaxis for HAE.
- In the HELP trial, approximately 70% of patients had a mean baseline attack rate of ≥ 2 attacks per month, but the majority of patients were not receiving routine prophylaxis over the assessment period. The proportion of patients experiencing ≥ 8 attacks per month was not reported for any of the trials.
- 6.16 Therefore, the PBAC considered that the trial populations lacked applicability to a population solely comprising patients with eight or more attacks per month.

Comparative effectiveness

HELP trial (lanadelumab vs placebo)

- 6.17 The primary and secondary efficacy end points, and the maximum severity of investigator confirmed HAE attacks from days 0-182, from the HELP trial are summarised in the figure below.

Figure 1: Primary and secondary efficacy end points and maximum severity of investigator confirmed HAE attacks from Days 0-182



All patients received injections every 2 weeks, with those in the every-4-week groups receiving placebo in between active treatments.

A. Attack rates are model-based mean attacks per month, with a month defined as 4 weeks. The mean attack rate for each group is presented with error bars representing 95% CI.

CI = confidence interval; HAE = hereditary angioedema.

Source: Figure 2, p2113 Banerji et al (2018).

B. Maximum hereditary angioedema attack severity is the most severe attack reported by the patient. For patients who did not complete the study, all available data were used for classification.

- 6.18 The submission stated that all three lanadelumab treatment regimens resulted in clinically meaningful and statistically significant percentage reductions in the least squares mean investigator confirmed HAE attack rate compared to placebo. This was reasonable. The number of both laryngeal and abdominal attacks were lower in all lanadelumab treatment arms compared to the placebo arm. This was also reflected in the results of the secondary efficacy endpoints; both the number of attacks requiring acute treatment per month, and the number of moderate to severe attacks per month over the treatment period, were also significantly lower in all of the lanadelumab treatment arms compared to the placebo arm.
- 6.19 The relative effectiveness of the three alternative lanadelumab treatment regimens was not assessed in the trial. As noted by the TGA clinical evaluator, while the primary and secondary analyses numerically favour the lanadelumab 300 mg q2wks arm over both the lanadelumab 150 mg q4wks and the lanadelumab 300 mg q4wks arms, the differences are small and the confidence intervals overlap considerably.
- 6.20 There were only limited data for the effectiveness of lanadelumab as routine prophylaxis for HAE, especially considering the intra- and inter-patient variability of both the frequency and severity of HAE attacks. Similarly, although there was a non-randomised extension study following the HELP trial, there was minimal evidence for the effectiveness of lanadelumab beyond 12 months of exposure, which is of particular concern given that it is proposed for long-term use.

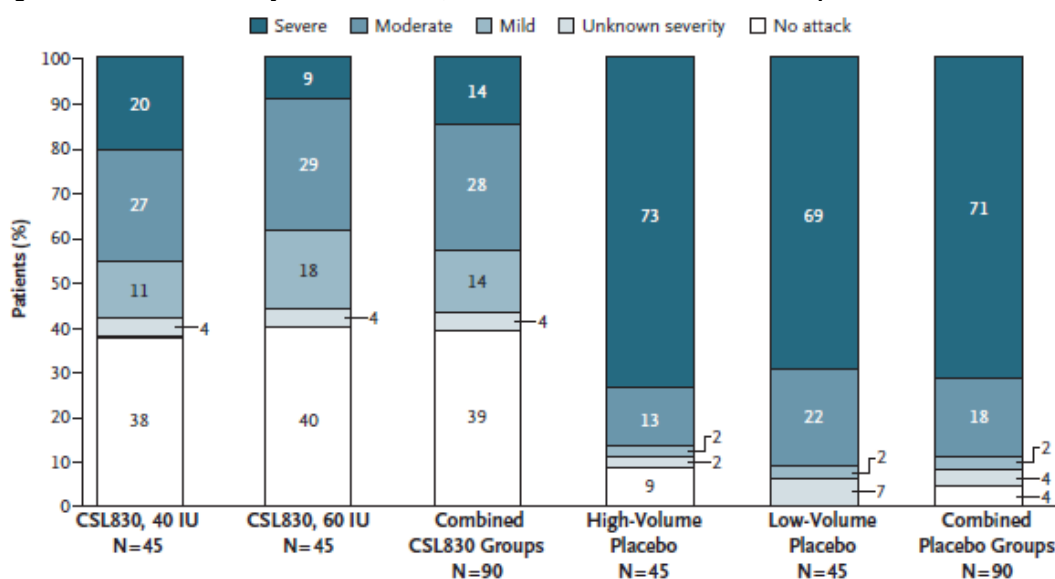
6.21 The submission stated that all lanadelumab dose regimens resulted in statistically significant and clinically meaningful improvements in the Angioedema Quality of Life questionnaire (AE-QoL) total score and across all domains except for fatigue/mood and nutrition scores. The results for each domain score, by treatment arm, showed separation of placebo from the lanadelumab arms over time in functioning and nutrition domains. The HELP trial ‘Patients Reported Outcomes Interim Report’ indicated that the analyses of covariance least squares mean difference versus placebo for AE-QoL were post hoc analyses; no multiplicity adjustment appears to have been made. There was no significant change in EuroQol 5-level descriptive system (EQ-5D) results.

COMPACT trial (SC C1-INH vs placebo)

6.22 The mean within-patient difference in the number of time-normalised HAE attacks per month, as compared with placebo, was -2.42 (95% CI: -3.38, -1.46) with 40 IU SC C1-INH twice weekly, and -3.51 (95% CI: -4.21, -2.81) with 60 IU SC C1-INH twice weekly.

6.23 The number of HAE attacks over weeks 3-16 of each treatment phase, according to the maximum severity of the attack, is summarised below.

Figure 2: Maximum severity of HAE attacks, over weeks 3-16 of each treatment phase.



CSL830 = SC C1-INH; HAE = hereditary angioedema

Note: the investigator graded the severity of each attack according to the intensity of the most severe symptom among the patients in the intention to treat population. Percentages may not total 100 because of rounding.

Source: Figure 1, p1137, Longhurst et al (2017).

CHANGE-B (IV C1-INH vs placebo)

6.24 The time normalised mean attack rates (standard deviation, SD) during the two 12-week crossover periods, were 6.1 (5.43) and 12.7 (4.80) attacks per 12 weeks for IV C1-INH and placebo treatments, respectively. The estimated difference in the number

of HAE attacks over 12 weeks of treatment with IV C1-INH compared with placebo was -6.60 (95% CI: -9.63, -3.57)⁷.

Indirect comparison

- 6.25 The submission presented a comparison of the results for the number of attacks per month and the number of uses of rescue medication across all three randomised trials during the treatment period (Table 5). As noted in the submission, and presented above in Table 4, the definition of the outcome evaluating the use of rescue medication was not consistent across the trials.
- 6.26 The submission considered that, given the lesser quality of the evidence in CHANGE-B and the uncertain applicability of the dose of IV C1-INH used in the trial, the COMPACT trial better informed a comparison with lanadelumab for both IV and SC C1-INH. The submission concluded that the data from the HELP and COMPACT trials suggested that the most effective doses in each trial, i.e. the lanadelumab 300 mg every 2 weeks regimen and the SC C1-INH 60 IU/kg twice weekly regimen, were reasonably comparable in terms of efficacy, both resulting in an 87% reduction in attacks compared to placebo (rate ratio for active treatment vs placebo of 0.13), and that reductions in rescue medication use were similarly reflective of the relative efficacy across the active treatments.

⁷ Calculated post hoc for the submission using RevMan software.

Table 5: Key results of the informal indirect comparison of efficacy of lanadelumab, SC C1-INH (Berinert SC) and IV C1-INH (Cinryze) as routine prophylaxis of acute HAE attacks

Trial	HELP			COMPACT		CHANGE-B	
	Lanadelumab		Placebo	SC C1-INH 60 IU/kg	Placebo	IV C1-INH 1,000 IU	Placebo
Treatment	300 mg q4wks	300 mg q2wks					
N	29	27	41	43	42	22	22
Run-in period attack rate –Number per month: Mean (SD) ^a							
During run-in period	3.7 (2.51)	3.5 (2.33)	4.0 (3.27)	4.0 (2.00)		NR	
Attack rate during treatment period (Day 0 to endpoint in HELP and CHANGE-B; Day 15-endpoint in COMPACT): Number per month^a							
Mean (95% CI)	0.53 ^b (0.36, 0.77)	0.26 ^b (0.14, 0.46)	1.97 ^b (1.64, 2.36)	0.52 ^c (0.00, 1.04)	4.03 ^c (3.51, 4.55)	2.03 ^d (1.28, 2.79)	4.23 ^d (3.56, 4.90)
Mean difference vs. PBO, (95% CI)	-1.44^{e,f} (-1.84, -1.04)	-1.71^{e,f} (-2.09, -1.33)	-	-3.51^g (-4.21, -2.81)		-2.20^{e,g} (-3.21, -1.19)	
Rate ratio vs. PBO, (95% CI)	0.27 (0.18, 0.41)	0.13 (0.07, 0.24)	-	0.13 ^h		0.48 ^h	
Mean % reduction vs. PBO, (95% CI)	73.3^h (59.5, 82.4)	86.9^h (76.2, 92.8)	-	87 ^h (84) ⁱ		52 ^h	
Rescue medication use during treatment period (Day 0 to endpoint in HELP and CHANGE-B; Day 15-endpoint in COMPACT): Number of uses per month^{a,j}							
Mean (95% CI)	0.42 ^b (0.28, 0.65)	0.21 ^b (0.11, 0.40)	1.64 ^b (1.34, 2.01)	0.32 (-0.33, 0.97)	3.89 (3.23, 4.55)	1.57 ^{d,k} (0.36, 2.77)	5.13 ^{d,k} (3.96, 6.30)
Mean difference vs. PBO, (95% CI)	-1.21^{e,f} (-1.59, -0.84)	-1.43^{e,f} (-1.79, -1.07)	-	-3.57^g (-4.50, -2.64)		-3.56^g (-5.24, -1.88)	
Rate ratio vs. PBO, (95% CI)	0.26 (0.16, 0.41)	0.13 (0.07, 0.25)	-	0.08 ^h		0.31 ^h	
Mean %reduction vs. PBO, (95% CI)	74.2^h (59.0, 83.7)	87.3^h (75.2, 93.5)	-	92 ^h (89) ⁱ		69 ^h	

C1-INH = C-1 esterase inhibitor; CI = confidence interval; IU = international units; IV = intravenous; NR = not reported; PBO = placebo; q2wks = every 2 weeks; q4wks = every 4 weeks; SC = subcutaneous.

^a No patient was permitted use of long-term oral prophylaxis use during to the run-in period or treatment period of the HELP trial. 1 patient used long-term oral prophylaxis during the run-in period and treatment period of the COMPACT trial; 13.6% of patients in CHANGE-B used long-term oral prophylaxis during the trial.

^b Results are from a Poisson regression model accounting for overdispersion; treatment group and normalised baseline attack rate were fixed effects in the model. The logarithm of time (days) each patient was observed during the treatment period was an offset variable.

^c Least square means as estimated from a mixed model

^d Data were reported as the number of attacks/uses of rescue medication for the 12-week active treatment and 1- week placebo treatment period. Monthly rates were calculated for the submission assuming one month = 28 days (4 weeks)

^e Post hoc analyses calculated for the submission using RevMan software. Note: as there were a number of errors in the results reported in Table 44 for this outcome for the HELP trial, the results from Table 23, p74 of the submission have been presented.

^f Across group difference

^g Within patient difference

^h Post hoc analyses calculated for the submission. Percentage reduction based on the rate ratio vs. PBO was calculated as 100% * (rate ratio - 1).

ⁱ Result reported in Table 2, p 1136 Longhurst et al (2017). The reduction in attacks was evaluated in 38 patients in the 40 IU group and 40 patients in the 60 IU group.

^j In the HELP trial, data reflect use of rescue medication for Investigator-confirmed attacks requiring acute treatment; there was some use of rescue outside of this and reported separately [Icatibant was used outside of an investigator-confirmed attacks by 4 subjects (1 in the PBO arm; 2 in the 150 mg q4wks arm; 1 in the 300 mg q4wks arm); complement C1-INH was used by 17 subjects (8 in the PBO arm; 1

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in the 150 mg q4wks arm; 4 in the 300 mg q4wks arm; 4 in the 300 mg q2wks arm – note use of C1-INH may have been for short term prophylaxis prior to a procedure, which was permitted by the protocol]; In the COMPACT trial data reflect any use of rescue medication which was permitted at any time; In CHANGE-B use of rescue medication reflects the number of infusions of open-label i.v.C1-INH required during attacks where use was deemed fit by investigator (double infusions were counted as 2 infusions)

^kThe number of patients who received double infusions could not be located during the evaluation.

Figures in bold indicate statistically significant results.

Source: Table 23, p74, Table 24, p77, Table 44, p118 and Table 45, p120 of the submission; Table 2, p2114 Banerji et al (2018).

Comparative harms

6.27 A summary of the key adverse events (AEs) in the HELP trial is provided below. 106 of 125 (84.8%) patients received all 13 planned doses of lanadelumab (26 weeks of treatment). The mean duration of treatment in weeks/days could not be located in the submission or the Clinical Study Report (CSR).

Table 6: Summary of key adverse events in the HELP trial

AE	Lanadelumab				Placebo N=41
	150 mg q4wks N=28	300 mg q4wks N=29	300 mg q2wks N=27	Total N=84	
	n (%)	n (%)	n (%)	n (%)	
Any TEAE	25 (89.3%)	25 (86.2%)	26 (96.3%)	76 (90.5%)	31 (75.6%)
Any treatment-related TEAE	17 (60.7%)	14 (48.3%)	19 (70.4%)	50 (59.5%)	14 (34.1%)
Any SAE	0 (0%)	3 (10.3%)	1 (3.7%)	4 (4.8%)	0 (0%)
Any treatment-related SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any severe (grade 3/4) TEAE	2 (7.1%)	4 (13.8%)	2 (7.4%)	8 (9.5%)	4 (9.8%)
Any treatment-related severe TEAE	0 (0%)	1 (3.4%)	0 (0%)	1 (1.2%)	1 (2.4%)
Any investigator reported AESI	1 (3.6%)	1 (3.4%)	3 (11.1%)	5 (6.0%)	0 (0%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinuation due to TEAE	0 (0%)	1 (3.4%)	0 (0%)	1 (1.2%)	1 (2.4%)

AE = adverse event; AESI = adverse event of special interest; q2wks = every 2 weeks; q4wks = every 4 weeks; SAE = serious adverse event; TEAE = treatment emergent adverse event

Source: Table 34, p92 of the submission.

6.28 Treatment-related AEs reported in ≥5% of patients receiving lanadelumab (with % of lanadelumab treated patients vs % of placebo treated patients) were: injection site pain (41.7% vs 26.8%), headache (7.1% vs 2.4%), injection site erythema (9.5% vs 2.4%) and injection site bruising (6.0% vs 0%).

6.29 The TGA evaluator concluded that lanadelumab appears to be well tolerated, but noted that only a small number of patients have been exposed and only for relatively short periods of time given that it is proposed for long-term use.

6.30 The key treatment emergent AEs in the COMPACT trial (SC C1-INH (Berinert) vs placebo) are summarised below. Adverse event data were pooled for the two placebo groups. The mean duration of treatment in the treatment periods where patients received SC C1-INH 60 IU/kg and 40 IU/kg were 16.0 and 16.3 weeks, respectively, and 15.3 weeks for all patients in the treatment periods where they received placebo.

Table 7: Summary of key adverse events in the COMPACT trial

	SC C1-INH			Placebo (total) N=86 n (%)
	40 IU/kg N=43 n (%)	60 IU/kg N=43 n (%)	Total N=86 n (%)	
Any TEAE	29 (67.4%)	30 (69.8%)	59 (68.6%)	57 (66.2%)
Any treatment-related TEAE	14 (32.6%)	15 (34.9%)	29 (33.7%)	22 (25.6%)
Any SAE	1 (2.3%)	0 (0.0%)	1 (1.2%)	2 (2.3%)
Any treatment-related SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Discontinuation due to TEAE	0 (0.0%)	2 (4.7%)	2 (2.3%)	1 (1.2%)
Death	0 (0.0%)	0 (0.0%)	0 (0%)	0 (0%)

C1-INH = C1-esterase inhibitor; IU = international units; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment emergent adverse event

Source: Table 38, p102 of the submission; US Food and Drug Administration Clinical Review Memo for Haegarda

- 6.31 In CHANGE-B (IV C1-INH (Cinryze) vs placebo), only one patient experienced an AE prior to exposure to IV C1-INH administered as either blinded routine prophylaxis or open-label rescue medication; all other AEs reported during the trial were pooled, regardless of whether patients were receiving blinded IV C1-INH or placebo at the time the AE occurred. This precluded any comparison with the other trials.
- 6.32 The submission also presented a comparison of the proportion of patients experiencing AEs across the trials, but noted that, given the differences in the designs of the trials, it was difficult to make any firm conclusions on the relative safety of lanadelumab, SC C1-INH and IV C1-INH. This was reasonable.

Clinical claim

- 6.33 The submission described lanadelumab as non-inferior in terms of efficacy and similar in terms of safety compared with IV C1-INH and the near market comparator SC C1-INH.
- 6.34 The submission claimed that, based on an informal indirect comparison of data from the HELP and COMPACT trials, by and large, the data suggested that the most effective doses, i.e., the 300 mg q2wks lanadelumab regimen and the SC C1-INH 60 IU/kg twice weekly regimen, were reasonably comparable in terms of efficacy.
- 6.35 The ESC and the PBAC considered that the claim of non-inferior efficacy was not adequately supported. The relative effectiveness of lanadelumab, SC C1-INH and IV C1-INH cannot be reliably determined based on the evidence presented in the submission due to the differences in design and conduct of the trials, the heterogeneity across the trial populations, the small sample sizes, and the inherent variability in both the frequency and severity of HAE attacks.
- 6.36 The ESC noted that the submission did not present any clinical evidence assessing the effectiveness of IV Berinert (the formulation available through the NBA) for routine prophylaxis of HAE attacks. The comparisons were versus SC Berinert and IV Cinryze and the pharmacokinetics / pharmacodynamics of the three formulations differ, while equi-effective doses between the three formulations have not been established. The submission did not present any clinical evidence in patients with HAE to support the

claim that the use of the data for SC C1-INH 60 IU/kg twice weekly as a proxy for IV Berinert 20 IU/kg twice weekly (the dosage that the submission claimed is most commonly used for HAE prophylaxis in Australia), is likely to be highly conservative.

- 6.37 Lanadelumab was superior to placebo when used for routine prevention of HAE attacks in the HELP trial population. There was no clear evidence of modification of the relative treatment effect by baseline HAE attack rate.
- 6.38 The submission stated that no firm conclusion can be made regarding the relative safety of lanadelumab compared with either IV C1-INH or SC C1-INH on the basis of the available data. The evaluation, the ESC and the PBAC considered this was reasonable.
- 6.39 The applicability of the evidence to the proposed PBS population for lanadelumab, and to the current patient population who are eligible for access to funded IV C1-INH for prophylaxis of HAE, was limited by differences in the line of therapy, and the baseline rate and severity of acute HAE attacks.
- 6.40 The ESC and PBAC noted that there are existing subsidised effective therapies for HAE prophylaxis and that a publication (the clinician survey) referred to in the PSCR stated:
- “Berinert for long term prophylaxis is used currently in the minority of HAE patients receiving prophylactic therapy. It is well tolerated with the majority of patients self-administering and its use has led to a reduction in acute treatment with icatibant” (Katelaris et al 2017)⁸, and
 - “As new HAE prophylactic therapies become available the medical profession must work together with the patient organisation and funding bodies to find a more satisfactory means of assessing the complexities surrounding HAE attacks rather than attack rate alone” (Katelaris et al 2017)⁹.
- 6.41 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.
- 6.42 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

- 6.43 The submission presented a CMA of lanadelumab versus IV C1-INH (Berinert) based on the claim of non-inferior effectiveness and similar safety. In addition to establishing non-inferior efficacy and safety, a cost-minimisation approach would need to establish that the cost per patient for treatment with lanadelumab would be no more than the

⁸ Katelaris CH, Perram F, et al. Hereditary angioedema attack prophylaxis management in Australian patients. *Internal Medicine Journal*. 2017; 47 (Suppl. 5):27.

⁹ Poster presentation of Katelaris CH, Perram F, et al. Hereditary angioedema attack prophylaxis management in Australian patients. *Internal Medicine Journal*. 2017; 47 (Suppl. 5):27.

cost per patient of IV C1-INH. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

6.44 The submission estimated that the equi-effective doses were:

- lanadelumab 300 mg q4wks in ■■■% of patients and 300 mg q2wks in ■■■% of patients; and
- IV C1-INH (Berinert) 20 IU/kg body weight twice weekly, with an average of 3.74 x 500 IU vials (1,870 IU) per dose based on the weight distribution of patients in the COMPACT trial.

Lanadelumab dosing: proportion of patients who down-titrate to q4wk

6.45 The lanadelumab Product Information recommends a starting dose of 300 mg q2wks, and that in patients who are attack free, a dose reduction to 300 mg lanadelumab q4wks may be considered. The submission noted that the PBAC Guidelines recommend assessing the impact of extrapolating dose titration if there is evidence that the trial was of inadequate duration for the doses to have reached steady state. As the HELP trial did not allow for dose flexibility, the submission used the proportion of patients who remained attack free in the HELP trial to estimate the proportion of patients who are candidates for extending the dosing interval to 4 weeks. As such, the ESC noted that the estimated proportion of patients receiving the reduced dose was not based on dosing in the trial, but was estimated based on the attack-free rate in the trial, which was, in turn, based on small patient numbers. While the PBAC Guidelines suggest that assessing the impact of extrapolating dose titration may be appropriate in certain circumstances, the evaluation and the ESC considered that the base case of the CMA should be based on the dose of the intervention on which the claim of non-inferiority was made, namely lanadelumab 300 mg q2wks. The considered this approach (using a trial-based equi-effective dose for lanadelumab of 300 mg q2wks) would be required to help ensure that the cost per patient for treatment with lanadelumab would be no more than the cost per patient at which C1-INH was considered to be cost-effective by MSAC.

6.46 The submission presented an analysis of the proportion of patients in the HELP trial who were attack free from days 0 to 70 and days 0 to 180 in each treatment group, to determine the probabilities of remaining attack free in days 70 to 180 conditional on attack free status at day 70 (Table 8). These results were uncertain due to the small numbers in most cells.

Table 8: Analysis of attack free periods as a proxy for opportunity to extend dosing of lanadelumab to q4wks

Trial period	Cohort	Attack free, n/N (%)				Notes
		300 mg q2wks	300 mg q4wks	150 mg q4wks	Any q4wks	
Day 0-180	All	12/27 (44.4%)	9/29 (31.0%)	11/28 (39.3%)	20/57 (35.1%)	Data from CSR
Day 70 to 180	All	21/27 (77.8%)	13/29 (44.8%)	15/28 (53.6%)	28/57 (49.1%)	Data from CSR
Day 0 to Day 70	All	13/27 (48.1%) [A]	11/29 (37.9%)	11/28 (39.3%)	22/57 (38.6%)	Calculated. 0 to 180-day result plus any patients with a first attack post day 70
Day 70 to 180	Attack free to day 70	(█) (%)	(█) (%)	(█) (%)	(█) (%) [B]	Used to derive patients with first attack between days 70 and 180
Day 70 to 180	Attack >0 to day 70	9/14 (64.3%) [C]	4/18 (22.2%)	4/17 (23.5%)	8/35 (22.9%)	Calculated, remainder patients

CSR = Clinical Study Report; q2wks = every 2 weeks; q4wks = every 4 weeks

Notes A, B, and C (located in the shaded cells of the table) are the data used to determine the proportion of patients expected to down-titrate to q4wks dosing in the long-term, and correspond to the decision analysis summarised in Figure 3.

Source: Table 63, p153 of the submission

6.47 The decision analysis used to determine the proportion of patients expected to down-titrate to q4wk dosing in the long-term is presented in Figure 3.



Source: Figure 30, p154 of the submission.

6.48 On this basis, the submission estimated that, at ‘steady state’, █% of patients would receive lanadelumab 300 mg q4wks (█), with the remaining █% receiving 300 mg q2wks. The ESC considered that there was no direct clinical evidence to support the submission’s assumption that the majority of patients would be able to reduce the dose of lanadelumab to every 4 weeks and remain on this dose over the long-term. Furthermore, this model predicts the expected maximum dose reduction that would occur if all patients actively attempted to minimise their effective dose. Given the reasonably good safety profile of lanadelumab, the relatively

convenient dosing regimen, and the potentially life-threatening nature of HAE attacks, patients may be reluctant to reduce the frequency of dosing, even where it may be clinically reasonable. The evaluation and the ESC considered that this was a major source of uncertainty in the CMA.

IV C1-INH dosing

- 6.49 The submission stated that there was an explicit assumption in the CMA that IV Berinert 20 IU/kg twice weekly (which the submission claimed is the dose used in Australian clinical practice) provides the same level of efficacy as SC C1-INH 60 IU/kg (the dose used in the COMPACT trial).
- 6.50 The submission argued that the use of data for SC C1-INH as a proxy for IV C1-INH was likely to be highly conservative, and that this assumption was supported by the results of a PK/PD modelling study reported by Zuraw et al (2017)¹⁰. The PK/PD model was used to simulate plasma profiles of C1-INH from first dose up to steady state, following q2wk dosing of 40 IU/kg SC, 60 IU/kg SC, 1,000 IU IV, or 2,500 IU IV. Only a conference abstract and poster presentation were available for this study.
- 6.51 Based on modelled simulations, it was predicted that the geometric mean trough concentration (C_{trough}) value after dosing with SC C1-INH 60 IU/kg would yield an 81% reduction in the relative risk of an HAE attack as compared with no treatment, and that the mean C_{trough} value after dosing with IV C1-INH 2,500 IU would yield a 65% reduction in the relative risk of an HAE attack. The submission argued that, for an individual weighing 80 kg, the 2,500 IU fixed dose of IV C1-INH represents a dose greater than 30 IU/kg; therefore, the assumption that IV C1-INH 20 IU/kg will result in the same reduction as SC C1-INH 60 IU/kg is conservative. The PK/PD model was not externally validated. Given the inherent intra- and inter-patient variability of both the frequency and severity of HAE attacks, and the limited data on which this model was based, the evaluation considered that the results should be interpreted with caution. The submission did not present any clinical evidence directly assessing the effectiveness of a fixed dose of 2,500 IU of IV C1-INH (Berinert) for prophylaxis of HAE attacks.
- 6.52 The CMA was based on a dosing regimen of 20 IU/kg twice weekly IV for estimating the cost of Berinert, on the basis that a survey of Australian clinicians experienced in treating HAE indicated that this was the most common regimen used in Australia¹¹ (IV Berinert is not TGA-registered for use as routine prophylaxis, so no dosing information is available in the Product Information for this indication).
- 6.53 The dose of Berinert used in the CMA (20 IU/kg twice weekly, resulting in 3.74 vials of

¹⁰ Zuraw BL, Cicardi M, et al. Pharmacokinetics and pharmacodynamics of subcutaneous versus intravenous C1-inhibitor for the prevention of hereditary angioedema attacks. *Annals of Allergy, Asthma and Immunology*. 2017; 119 (5):S40.

¹¹ Katelaris CH, Perram F, et al. Hereditary angioedema attack prophylaxis management in Australian patients. *Internal Medicine Journal*. 2017; 47 (Suppl. 5):27.

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500 IU per patient per dose) was higher than the dose of Cinryze used in the CHANGE-B trial (1,000 IU fixed dose twice weekly, resulting in 2 vials of 500 IU per patient per dose), which was the key trial on which the MSAC based its assessment of the cost-effectiveness of C1-INH. As a CMA, the ESC considered that the cost per patient for lanadelumab should be no more than the cost per patient at which MSAC considered Cinryze to be cost-effective, including any price reductions realised through the NBA tendering arrangements.

6.54 The pre-PBAC response (p2) stated that “due to dosing differences between Cinryze and Berinert IV, it is likely the Commonwealth and State Governments are currently paying more for IV C1-INH treatment than what MSAC considered acceptably cost-effective”. To address this, the pre-PBAC response proposed an RSA to “provide certainty that each patient is treated in a cost-effective manner”.

Results of cost-minimisation analysis

6.55 The results of the submission’s cost-minimisation analysis are presented in Table 9.

Table 9: Result of the cost-minimisation analysis (base case)

Component	Lanadelumab	IV C1-INH (Berinert)
Cost per dose	\$ [REDACTED]	\$3,454
Administrations per year	[REDACTED]	104
Total medicine cost per year	\$ [REDACTED]	\$359,211 ^b
Total medicine cost per week	\$ [REDACTED]	\$6,908
Difference in cost per year ^a		-\$ [REDACTED] ^c
Difference in cost per week ^a		-\$ [REDACTED] ^c

C1-INH = C1-esterase inhibitor; IV = intravenous

^a Assumes [REDACTED] % of patients receive lanadelumab 300 mg q4wks (13 doses per year), [REDACTED] % 300 mg q2wks (26 doses per year)

^b Assumed dose of 20 IU/kg, weighted average of 3.74 x 500 IU vials per dose based on the weight distribution of patients in the COMPACT trial

^c Cost of lanadelumab compared with cost of IV C1-INH

Source: Section 3.4.1 of the submission; Excel workbook ‘TAKHZYRO_Section_3_Final’

6.56 The submission acknowledged that the main sources of uncertainty in the cost-minimisation analysis were the proportion of patients receiving the lower dose of lanadelumab (300 mg q4wks), and the dosing of IV Berinert. The submission assessed the impact of these uncertainties on the financial implications, but not on the economic analysis. The impact of the proportion of patients who are assumed to receive the lower dose of lanadelumab on the cost of lanadelumab per patient is presented in the table below.

Table 10: Sensitivity analysis: proportion of patients dosed with lanadelumab every 4 weeks

% of patients on LANA q4wks	Lanadelumab 300 mg			
	[REDACTED] % (base case)	50%	25%	0% (per trial)
Proposed cost per dose	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Administrations per year	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total medicine cost per year	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost per dose of LANA required to match cost of IV C1-INH (Berinert) 20 IU/kg				
Cost lanadelumab 300 mg	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
% price reduction required	-	[REDACTED] %	[REDACTED] %	[REDACTED] %

C1-INH = C1-esterase inhibitor; IU = international units; IV = intravenous; LANA = lanadelumab

Source: Section 3.4.1 of the submission; calculated during evaluation based on Excel workbook ‘TAKHZYRO_Section_3_Final’

6.57 As noted above, the ESC considered that the equi-effective doses nominated by the submission were not appropriate and significantly overestimated the price of lanadelumab because:

- the CMA should be based on the dose of lanadelumab on which the claim of non-inferiority was made (lanadelumab 300 mg q2wks, 0% on q4wk dose), and
- for the population defined by MSAC, the cost per patient for lanadelumab should be no more than the cost per patient at which MSAC considered Cinryze to be cost-effective, including any price reductions realised through the NBA tendering arrangements.

6.58 The PBAC agreed with the concerns raised by the ESC in the paragraph above, but considered the overarching issue was that a cost-minimisation analysis was inappropriate as outlined in Paragraph 7.10.

Drug cost/patient/year

6.59 The cost/patient/year for lanadelumab was \$ [REDACTED]. This was based on the assumption that [REDACTED]% of patients would receive a steady state dose of 300 mg q4wks and [REDACTED]% would receive 300 mg q2wks, at a cost of \$ [REDACTED] per dose. The dose on which the non-inferiority claim was based was 300 mg q2wks. The cost/patient/year for IV C1-INH (Berinert) was estimated as \$359,211. This was based on a dose of 20 IU/kg body weight and the weight distribution for the COMPACT trial population, giving a weighted average of 3.74 x 500 IU vials per dose, at a cost of \$924.20 per vial.

Table 11: Drug cost per patient for lanadelumab and C1-INH

	Lanadelumab			C1-INH (Berinert)		
	Trial dose ^a	Model	Financial estimates	Trial dose	Model	Financial estimates
Mean dose	300 mg q2wks ^a	[REDACTED]% 300 mg q2wks [REDACTED]% 300 mg q4wks	300 mg q2wks for 6 months, then [REDACTED]% q2wks [REDACTED]% q4wks	60 IU/kg SC Berinert twice weekly ^{a,e}	1,869 IU ^g 20 IU/kg IV C1-INH (Berinert) twice weekly	1,869 IU ^g 20 IU/kg IV C1-INH (Berinert) twice weekly
Mean doses/patient/year	26.0 ^a	[REDACTED]	1 st year: [REDACTED] Subsequent years: [REDACTED]	104	104	104
Cost/patient/month	\$ [REDACTED] ^b	\$ [REDACTED] ^b	\$ [REDACTED] / [REDACTED] ^{b,c,d}	NA ^f	\$29,934 ^b	\$29,934 ^b
Cost/patient/year	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED] / [REDACTED] ^{c,d}	NA ^f	\$359,211	\$359,211

C1-INH = C1-esterase inhibitor; IU = international units; IV = intravenous; NA = not applicable; q2wks = every 2 weeks; q4wks = every 4 weeks; SC = subcutaneous

^a Dose on which the non-inferiority claim was based

^b Cost/patient/year divided by 12

^c Cost/patient in first year of treatment/subsequent years of treatment.

^d The difference in the cost per patient in subsequent years of treatment in the financial estimates and that in the model was due to rounding of the percentage of patients assumed to receive treatment every 4 weeks in the financial estimates.

^e The mean dose was not reported

^f Berinert SC is not currently publicly funded in Australia

^g Weighted average of 3.74 x 500 IU vials per dose based on the weight distribution of patients in the COMPACT trial. Mean number of IU of C1-INH per dose calculated as 3.74 x 500 IU.

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Note: The proposed price for 300 mg of lanadelumab was \$[REDACTED]. The cost of a 500 IU vial of Berinert is \$924.20.
Source: Table 19, p62, Table 60, p149, Section 3.2, pp150-4 of the submission; Excel workbooks 'TAKHZYRO_Section_3_FINAL' and TAKHZYRO_Section_4_FINAL'.

Estimated PBS usage & financial implications

- 6.60 This submission was not considered by Drug Utilisation Sub-Committee. The submission stated that the proposed PBS patient population for lanadelumab was expected to be the same as the patient population currently receiving C1-INH as routine prophylaxis, and used a market share approach to estimate the number of eligible patients for lanadelumab, based on the current utilisation of IV C1-INH reimbursed through the NBA (using NBA supply data from July 2017 to January 2019).
- 6.61 All patients were assumed to receive lanadelumab 300 mg every 2 weeks for 26 weeks when they initiate therapy. Subsequently, it was assumed that [REDACTED]% of patients would receive a 'steady state' dose of 300 mg q4wks (13 doses per year), with the remainder receiving 300 mg q2wks (26 doses per year). Thus, patients were assumed to receive an average of [REDACTED] doses ($[REDACTED]\% \times (26+13)/2 + [REDACTED]\% \times 26$) in the year of initiation, and [REDACTED] doses ($[REDACTED]\% \times 13 + [REDACTED]\% \times 26$) in continuing years. The evaluation, ESC and PBAC considered that this assumption was poorly supported. This was a major source of uncertainty in the financial estimates.
- 6.62 The estimated overall net implications of listing lanadelumab to the PBS/RPBS and the net financial implications for the Australian Government health budget are summarised in Table 12. The submission noted that the NBA (through which Berinert is accessed) is funded by both the federal government (63%) and state and territory governments (37%).

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Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimate of C1-INH market (extrapolated from NBA supply data for July 2017 to January 2019)						
C1-INH vials issued by NBA ^a						
C1-INH patient-years ^b						
Estimated extent of use of lanadelumab						
Expected uptake	%	%	%	%	%	%
Number of patients treated						
Number of scripts dispensed ^c						
Estimated financial implications of lanadelumab						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Net financial implications for the Australian Government health budget						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Other federal health care costs ^d	-\$	-\$	-\$	\$	-\$	-\$
Net cost to Australian federal Government	\$	\$	\$	\$	\$	\$
State/territory governments	-\$	-\$	-\$	-\$	-\$	-\$
Net impact - all federal/state/territory budgets	\$	\$	\$	\$	-\$	-\$

^a Based on supply data from the NBA: In 2018 (calendar year), the NBA supplied [redacted] vials (for all indications). This was extrapolated by the submission, with the submission estimating there would be [redacted] vials supplied in 2019 and [redacted] in 2020 (Year 1).

^b The submission assumed each patient receives [redacted] vials per year of IV C1-INH (3.74 vials per dose, [redacted] doses per year)

^c Assuming an average of [redacted] scripts per patient in the first year of treatment and [redacted] scripts per patient per year in subsequent years of treatment, as estimated by the submission.

^d Cost to the Australian Government for funding of IV C1-INH through the National Blood Authority (NBA), assuming the federal government is responsible for 63% of funding and state/territory governments are responsible for the remaining 37%.

Source: Table 70, p162, Table 72, p163, Table 73, p166 and Table 74, p166 of the submission.

The redacted table shows that at Year 6, the net cost to the PBS would be \$20 - \$30 million.

6.63 The estimated net cost to all government health budgets (Commonwealth and State/Territory) declined from an annual cost of less than \$10 million in Year 1 to an annual saving of less than \$10 million in Year 6. Listing of lanadelumab would result in a cost-shifting from the NBA to the PBS/RPBS. The variation in the net impact over the six years was due to the submission's assumption that the number of patients initiating treatment with lanadelumab would be highest in the first few years of listing ([redacted] patients in Year 1, declining to only [redacted] patients in Years 3-6), and because all initiating patients were assumed to receive the higher dose of lanadelumab (300 mg q2wks) for the first 6 months of therapy, while [redacted]% of patients were assumed to receive the reduced dose of 300 mg q4wks over the longer term.

6.64 The evaluation, ESC and the PBAC considered that the average cost per patient of lanadelumab could be significantly higher than assumed in the submission if a greater proportion of patients remain on the higher dose of lanadelumab.

6.65 The evaluation and the ESC considered that the submission's estimation of the number of patients likely to be treated was not reliable given:

- The assumption that all current utilisation of IV C1-INH (Berinert) is for routine prophylaxis of HAE attacks, when the NBA data also included the use of IV C1-INH for the treatment of acute attacks and pre-procedural prophylaxis;
 - The potential for listing of lanadelumab to result in growth of the market for routine prophylaxis of HAE attacks due to the ease of administration. The evaluation and the ESC considered that some HAE patients who are eligible for routine prophylaxis with IV C1-INH may not be accessing this therapy due to the requirement for twice weekly IV infusions. These patients may be more willing to receive subcutaneous injections of lanadelumab every 2-4 weeks; and
 - The actual number of patients who are eligible under the NBA criteria is unclear as there may be some leakage in patients with fewer than eight attacks per month.
- 6.66 The PBAC agreed with the issues raised by the ESC in the paragraph above, but considered an overarching issue is that the appropriate clinical role for lanadelumab is broader than the population who are eligible for IV C1-INH.
- 6.67 The submission's estimates of the number of patients treated with lanadelumab (■ to ■ per year) were considerably higher than the estimated number of patients likely to receive routine prophylaxis with IV C1-INH in the MSAC assessment of IV C1-INH for routine prophylaxis of HAE (approximately 8 per year).
- 6.68 The PSCR argued that the treated HAE population was underestimated in the MSAC assessment, which was based on limited data and required assumptions to derive the estimated number of patients likely to access IV C1-INH. The PSCR referred to a survey of 14 Australian specialists (of whom 13 responded) which found that 18 patients had been prescribed IV C1-INH as prophylaxis.¹² The PSCR claimed that the survey did not include all specialists in Australia who treat patients with HAE, and thus 18 patients was likely to be an underestimate. However, only limited details were available about the survey (e.g. it was unclear whether all 18 patients were receiving IV C1-INH prophylaxis at the time of the survey, or whether this was the number of patients who had received prophylaxis with IV C1-INH at some point over the course of their care). The ESC considered that the actual number of patients using C1-INH for routine prophylaxis is unknown, but based on vial usage as per the NBA's data, is likely to be much higher than the MSAC estimates.
- 6.69 The submission's estimate of utilisation was based on the number of vials of IV C1-INH supplied through the NBA, however the PSCR implied that there is leakage of IV C1-INH in patients who experience fewer attacks than specified in the NBA criteria.

¹² Poster presentation of Katelaris CH, Perram F, et al. Hereditary angioedema attack prophylaxis management in Australian patients. *Internal Medicine Journal*. 2017; 47 (Suppl. 5):27.

Number of patients who experience ≥8 acute HAE attacks per month

- 6.70 The DUSC ‘Icatibant: 24 month predicted versus actual analysis’ (June 2015) showed that 8 patients received 25 or more vials (pre-filled syringes) of icatibant over a 12 month period (among patients who commenced from August 2012 to December 2013 and were followed up until December 2014). The submission stated that the number of injections is considered a reasonable proxy for the number of treated attacks (though it may overestimate the number of treated attacks as the DUSC analysis stated that the average attack requires 1.12 vials and some patients may have multiple supplies on hand).
- 6.71 However, the submission argued that the DUSC analysis represents use of icatibant early in its listing on the PBS, when specialists and patients were less familiar with the drug and therefore less likely to use it in comparison to today. Thus, the submission argued that the DUSC analysis may underestimate the use of icatibant. To support this, the submission used a 10% PBS sample and reported that 30 patients had 20 or more vials of icatibant supplied over the 12 month period from October 2015 to September 2016 (prior to the availability of IV C1-INH through the NBA), decreasing to 20 patients in the period from October 2017 to September 2018 (after IV C1-INH was subsidised for acute attacks and routine prophylaxis). The submission acknowledged this analysis was based on a small number of patients (25 patients up-scaled to 250 patients). In addition, the submission did not provide sufficient information about the methodology of the 10% PBS sample to enable evaluation.
- 6.72 The thresholds used in the DUSC analysis and the submission’s 10% PBS sample were 20 to 25 vials in a 12 month period, which would include patients with as few as 1.7 to 2 treated attacks per month, rather than 8 or more attacks per month. (Further, icatibant utilisation may not represent a reliable proxy for determining the number of patients with very frequent attacks as the Product Information for icatibant states “in clinical trials, not more than 8 injections of icatibant per month have been administered”).
- 6.73 The ESC considered that the actual number of patients who are eligible for and using IV C1-INH in accordance with the NBA criteria is not known but, based on available data from the DUSC analysis of icatibant, is likely to be fewer than the treated population estimated in the submission (■ to ■ patients per year).

Financial Management – Risk Sharing Arrangements

- 6.74 The submission stated that the sponsor was willing to consider appropriate risk sharing arrangement (RSA) proposals. The PSCR (p4) stated that “if the frequency of dosing of lanadelumab remains a key uncertainty for the PBAC, then it is proposed that this could be addressed with a limit on expenditure per patient per year or other appropriate RSA”. The ESC noted that, as there is no reliable information regarding the number of patients eligible for IV C1-INH as prophylaxis in accordance with the NBA restriction, any listing based on a CMA would expose the Australian Government to considerable financial risk.

- 6.75 In addition to the above, the pre-PBAC response (p2) proposed that an RSA could also be based on the original annual cost per patient at which MSAC considered Cinryze to be cost-effective “to provide certainty that each patient is treated in a cost-effective manner”.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcomes

- 7.1 The PBAC did not recommend the listing of lanadelumab as routine prophylaxis of recurrent attacks of HAE. The PBAC considered the clinical need, and appropriate clinical role of lanadelumab, to be broader than that for IV C1-INH, and as such, the cost-minimisation analysis versus C1-INH presented in the submission was uninformative. The PBAC further considered the number of patients meeting the NBA criteria for prophylactic treatment with C1-INH, as well as the size of the broader population, to be uncertain.
- 7.2 The PBAC acknowledged the debilitating nature of HAE attacks, with the consumer comments describing the attacks as painful, unpredictable and potentially life-threatening. The hearing and consumer comments outlined that, given the severity of HAE attacks and the adverse effects and lack of efficacy associated with danazol, there is a clinical need for effective and tolerable prophylactic therapies in patients who experience fewer than eight attacks per year (i.e. patients who do not meet the current NBA criteria for IV C1-INH).
- 7.3 Further, the consumer comments described the difficulties associated with twice-weekly IV administration of Berinert IV. The PBAC considered that a subcutaneous formulation would overcome most of the administration issues, and noted that subcutaneous Berinert (‘Berinert SC’) was recently registered by the TGA, although it is not funded by the NBA.
- 7.4 The PBAC noted that C1-INH (Berinert IV) is restricted to patients with very severe HAE, as the MSAC advised that C1-INH would only be cost-effective in patients who experience eight or more attacks per month. The PBAC noted that the MSAC’s assessment of the cost-effectiveness of C1-INH for routine prophylaxis appeared to have used the price proposed for the acute attack indication (which was cost-minimised against icatibant; p1, MSAC Public Summary Document for C1-IH for HAE, Application 1394). The MSAC Public Summary Document states that MSAC ‘concluded that it had low confidence that the use of C1-INH offered clinically important improvements for pre-procedural and routine prophylaxis of hereditary angioedema’ (p2), and its recommendation was based on ‘restricting access to only those patients with a very high attack frequency’, which the MSAC estimated would be limited to 8 patients per year (pp 8 and 13).
- 7.5 The PBAC noted that the submission requested listing of lanadelumab in a broader population than the NBA criteria for IV C1-INH, and considered a broader listing would align with the consumer view that there is a clinical need for effective prophylactic

therapies in patients who experience fewer than eight attacks per year. The PBAC considered the clinical role of lanadelumab in the context of this clinical need, the ease of administration of a SC formulation and the clinical evidence for lanadelumab which likely included a large proportion of patients who experienced fewer than eight attacks per month at baseline. As such, the PBAC advised that the appropriate clinical role for lanadelumab is broader than the population who are eligible for IV C1-INH.

- 7.6 The PBAC noted that the PSCR stated that an alternative option would be to list lanadelumab with the same wording as the NBA access criteria (i.e. 'second line, as routine prophylaxis for patients who experience the equivalent of eight or more acute attacks per month'). However, as outlined above, the PBAC considered that the appropriate clinical role for lanadelumab is broader than the population who are eligible for C1-INH.
- 7.7 The PBAC considered that, in light of its advice that a broader listing (than that which applies to IV C1-INH through the NBA) would be appropriate, C1-INH was not the appropriate comparator. The PBAC considered that standard of care (on-demand treatment plus oral routine prophylaxis) was the appropriate comparator in patients who experience fewer than eight attacks per month, which the PBAC considered would represent the majority of patients with a broader listing.
- 7.8 The PBAC considered that the relative effectiveness and safety of lanadelumab and SC C1-INH and IV C1-INH could not be reliably determined due to differences in the design and conduct of the trials used in the indirect comparison, the heterogeneity across the trial populations, the small sample sizes, and the inherent variability in the frequency and severity of HAE attacks. Further, the PBAC noted that no clinical evidence was presented assessing the effectiveness of the formulation of IV C1-INH available through the NBA (IV Berinert) and noted the different formulations have different pharmacokinetics and pharmacodynamics. Overall, the PBAC considered that the claim of non-inferior effectiveness and safety versus SC C1-INH and/or IV C1-INH was not adequately supported by the evidence presented in the submission.
- 7.9 Further, the PBAC considered that the clinical trial of lanadelumab (the HELP trial) lacked applicability to a population solely comprising patients with eight or more attacks per month. That is:
- The HELP trial enrolled patients who had experienced at least one HAE attack per 4 weeks;
 - The mean number of attacks at baseline was 3.2 to 4 attacks per 4 weeks; and
 - The proportion of patients in the HELP trial who experienced eight or more attacks at baseline was unknown (and only 5.6% of patients were receiving danazol). However, the PBAC noted that in the placebo arm of the HELP trial, the median attack rate during the treatment period was 1.7 attacks per month, with a maximum HAE attack rate of 8.3 per month.
- 7.10 The PBAC considered that a cost-minimisation analysis was inappropriate given: the

indirect evidence presented did not demonstrate non-inferior effectiveness of lanadelumab versus C1-INH (SC or IV); and the PBAC's advice that the appropriate clinical role of lanadelumab is broader than the population in whom C1-INH was considered cost-effective by MSAC.

- 7.11 The PBAC considered that the number of eligible patients who access IV C1-INH for routine prophylaxis was uncertain given the lack of data about utilisation by indication and the potential for leakage in patients who experienced fewer than eight attacks per month. The PBAC advised that more comprehensive information regarding utilisation of IV C1-INH through the NBA would be informative, including data regarding the indication for use and patient eligibility.
- 7.12 The PBAC noted that the financial estimates were based on utilisation of IV C1-INH through the NBA. The PBAC considered that the financial estimates would need to be revised to account for use in a broader population.
- 7.13 The PBAC considered that the financial estimates had underestimated the number of vials per patient because it relied on the assumption that ■% of patients would only require a steady state dose of lanadelumab 300 mg every 4 weeks.
- 7.14 The PBAC considered that any resubmission would need to be a major resubmission and would need to:
- Include a broader population than outlined in the NBA criteria for IV C1-INH;
 - Be based on a cost-utility analysis versus standard of care; and
 - Include revised financial estimates to account for listing in a broader population. The financial estimates should also be based on a significantly lower proportion of patients using the reduced dosing regimen (per Paragraph 7.13).
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Shire (now part of Takeda) will work with the Department of Health and the PBAC so that patients with this rare disease are able to access lanadelumab prophylaxis in Australia.