22 November 2018
EMA/809232/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Takhzyro (recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein)
Treatment of hereditary angioedema
EU/3/15/1551 (EMA/OD/075/15)
Sponsor: Shire Pharmaceuticals Ireland Limited

Note

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

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1. Product and administrative information

Product	
Active substance	Recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein
International Non-Proprietary Name	Lanadelumab
Orphan indication	Treatment of hereditary angioedema
Pharmaceutical form	Solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	B06AC05
Sponsor's details:	Shire Pharmaceuticals Ireland Limited Block 2 & 3 Miesian Plaza 50 – 58 Baggot Street Lower Dublin 2 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Dyax Ltd
COMP opinion date	3 September 2015
EC decision date	9 October 2015
EC registration number	EU/3/15/1551
Post-designation procedural history	
Transfer of sponsorship	Transfer from Dyax Ltd to Shire Pharmaceuticals Ireland Limited – EC decision of 16 November 2017
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	K. Dunder, J. Emmerich
Applicant	Shire Pharmaceuticals Ireland Limited
Application submission date	12 March 2018
Procedure start date	29 March 2018
Procedure number	EMA/H/C/004806/0000
Invented name	Takhzyro
Therapeutic indication	Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. Further information on Takhzyro can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports
CHMP opinion date	18 October 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	M. Možina/ D. Matusevicius
Sponsor's report submission date	16 August 2018
COMP discussion and adoption of list of questions via written procedure	18 September 2018
Oral explanation	10 October 2018
COMP opinion date	26 October 2018

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2015 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein was considered justified based on preliminary clinical data showing reduction of angioedema attack rates in treated patients;
- the condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia;
- the condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.
- In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a reduction in angioedema attack rates comparing favourably with the data reported for existing products. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by hereditary angioedema.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The therapeutic indication “Takhzyro is indicated for routine prevention of attacks of hereditary angioedema (HAE) in patients aged 12 years and older” falls within the scope of the designated orphan indication “treatment of hereditary angioedema”.

Angioedema is oedema of the deep dermis and subcutaneous tissues. It is usually an acute mast cell–mediated reaction caused by exposure to drug, venom, dietary, pollen or animal dander allergens. Angioedema can also be an acute reaction to ACE inhibitors, a chronic reaction, or a hereditary or an acquired disorder characterized by an abnormal complement response. The main symptom is swelling, which can be severe. Diagnosis is by examination.

Acute angioedema is mast cell–mediated in > 90% of cases. Mast cell–mediated mechanisms include acute allergic, typically IgE-mediated reactions. IgE-mediated angioedema is usually accompanied by acute urticaria. It may often be caused by the same allergens (e.g., drug, venom, dietary, extracted allergens) that are responsible for acute IgE-mediated urticaria.

The cause of chronic (> 6 weeks) angioedema is usually unknown. IgE-mediated mechanisms are rare, but chronic ingestion of an unsuspected drug or chemical (e.g., penicillin in milk, a non-prescription drug, preservatives, other food additives) is sometimes the cause. A few cases are due to hereditary or acquired C1 inhibitor deficiency.

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified. Please see EPAR scientific document.

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of the condition since the time of orphan designation. HAE is unpredictable in nature with substantial variation in the frequency and the age of onset of attacks. Attack patterns vary with age and may affect a single site or multiple sites. Patients with symptomatic HAE generally experience at least one acute exacerbation per month. Most attacks of HAE last 2 to 5 days, resulting in 20 to 100 days of incapacitation per year. Acute episodes of HAE often occur without warning and often may be precipitated by a trigger.

The mortality rate from undiagnosed HAE can be as high as 40% and is primarily attributed to upper airway obstruction. Asphyxiation can occur in 20 minutes to 14 hours in patients of any age, and it has occurred in patients with no previous history of respiratory symptoms (NORD Guide on Hereditary Angioedema).

Number of people affected or at risk

The prevalence of HAE calculated at the time of orphan designation in 2015 included Types I & II of hereditary angioedema (HAE), characterized by C1-INH deficiency, and it was estimated at 0.2 in 10,000.

The Sponsor completed an updated review of the prevalence using more recent literature. A third category previously referred to as 'HAE Type III', has been more recently described as HAE with normal C1 INH, with subsets of FXII-HAE and U-HAE (Cicardi et al., 2014) The largest study to date reported 265 patients seen at a clinic in Germany, giving a prevalence of 0.03 per 10,000, using 2017 German population estimates. However, without explaining their calculations, the authors estimated a prevalence of 0.10 per 10,000 (Bork, Wulff, Witzke, & Hardt, 2015). In other studies the prevalence ranged from 0.01 (Slovakia) to 0.02 (Italy) (Bova et al., 2017; Jesenak et al., 2017).

Taking the upper levels of prevalence reported in the most recent literature into account, the total prevalence for all categories of HAE proposed by the applicant was 0.27 in 10,000, which was approximated by the COMP to less than 0.5 in 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

As described by the sponsor, two approaches are currently used in the management of hereditary angioedema: acute or 'on-demand' treatment of angioedema attacks, and prevention of angioedema attacks with short or long-term prophylactic therapy.

The currently authorized medicinal products in the EU include C1-INH replacement products such as human plasma-derived C1-INH (pdC1-INH) concentrates (Cinryze, Berinert and Cetor) or recombinant human C1-INH (Ruconest), and products acting on the kallikrein pathway such as icatibant (Firazyr), acting as bradykinin B2 receptor antagonist. Conjugated androgens, such as danazol, and

antifibrinolytics, such as ε-aminocaproic acid and tranexamic acid, are frequently used for the prophylaxis of acute attacks and are licensed in some but not all Member States.

Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (adults, adolescents and children 2 years and older) with C1-esterase-inhibitor deficiency but not for prophylaxis of HAE attacks. Among the C1-INH replacement products, Cinryze is centrally authorized (in addition to treatment and pre-procedure prevention of angioedema attacks) also for routine prevention of the attacks in patients with severe and recurrent attacks, who are intolerant to or insufficiently protected by oral prevention treatments (tranexamic acid), or patients who are inadequately managed with repeated acute treatment. A subcutaneous formulation of Berinert, a plasma-derived C1-INH, was recently approved for the prevention of HAE in EU through the decentralised procedure. The procedure involved 22 member states. This formulation is given by subcutaneous injection twice weekly and is marketed in the US under the tradename Haegarda and in Europe as BERINERT 2000/3000.

Cinryze requires IV infusion every three or four days due to its short half-life, and may necessitate the placement of an indwelling catheter. Plasma-derived C1-INH has class warnings including hypersensitivity, thromboembolic events, and viral safety (risk of transmission of infectious agents) due to its plasma derivation.

Current treatment guidelines recommend against the use of antifibrinolytics for long-term prophylaxis (LTP) due to limited efficacy. The treatment guidelines recommend C1-INH or attenuated androgens as standard of care to prevent HAE attacks. However, there are numerous contraindications, therapeutic class adverse events (AEs), risk factors for AEs, tolerance to therapy, and overall suboptimal control of HAE due to the need higher or more frequent dosing, threat of breakthrough attacks, and low attack-free rates. Attenuated androgens (e.g. danazol, stanozolol, and oxandrolone) however increase hepatic production of C1 INH protein and are limited by safety issues, including seborrhea, altered libido, muscle pains and cramps, headache, nervousness, emotional lability, depression, fatigue, menstrual abnormalities, and masculinization, and lack definitive efficacy evidence at currently recommended lower doses.

The current recommendations for long-term prophylaxis state that:

- Prophylaxis should be considered for patients who face events in life that are associated with increased disease activity, and that patients should be continually evaluated for long-term prophylaxis.
- C1-INH is recommended as first-line long-term prophylaxis, and androgens are recommended as second-line prophylaxis.
- Adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease.

In spite of available medicinal products for the treatment of acute attacks, HAE still is a disorder with high mortality. Although existing preventive therapy with C1-INH ameliorates the number and severity of attacks, some patients still experience breakthrough attacks.

Significant benefit

The sponsor claimed significant benefit versus the authorized treatments based on grounds of improved efficacy and of major contribution to patient care.

The significant benefit claims are in relation to those treatments that are currently authorized for the same indication, i.e. for the prevention of HAE attacks, namely the C1-INH plasma-derived Cinryze and

Berinert 2000/3000, and the anticoagulant tranexamic acid. Tranexamic acid however was not taken into account in the sponsor's discussion, as it is not widely used. In addition, the most recent WAO & EAACI guidelines recommend C1-INH as first-line long-term prophylactic therapy (androgens as second-line), while antifibrinolytics are not recommended due to the lack of efficacy in long-term prophylaxis (Maurer et al., 2018). The use of attenuated androgens is limited by safety issues, lack of definitive efficacy information at recommended doses, and a restricted patient population that can benefit. The active substance of Takhzyro, lanadelumab, is a recombinant fully human IgG1 monoclonal antibody inhibitor of active plasma kallikrein (pKal), binding both soluble and membrane-bound forms of the enzyme. It is hypothesized that by specifically inhibiting pKal, lanadelumab prevents the release of bradykinin thereby preventing the vascular leak and swelling that is initiated when bradykinin binds to the B2 receptor.

Improved efficacy

The claims of improved efficacy versus C1 INH factors used for prophylactic treatment were based on indirect comparison of the Takhzyro trials with those of Cinryze and Berinert 2000/3000, as no direct comparison data are available.

The study designs between the pivotal studies for CINRYZE and the recently approved use of BERINERT 2000/3000 for prophylaxis differ, and the sponsor presented two tables showing the main characteristics of the pivotal trial of Takhzyro next to the pivotal trial of Cinryze (table 2) and Berinert (table 3).

Table 1. Lanadelumab (Takhzyro) and Cinryze pivotal trials

	Lanadelumab	CINRYZE
Study Design	Randomized, double-blind, parallel group, placebo comparator	Randomized, double-blind, placebo-controlled, crossover
Sample Size	126 randomized; 125 treated; 113 completed	24 randomized; 22 treated; 22 completed
Study Population	90.4% Type I HAE 9.6% Type II HAE	81.8% Type I HAE 18.2% Type II HAE
Mean Age (range)	40.7 (12, 73) years	38.1 (9, 73) years
Percentage Female / White	70.4% / 90.4%	90.9% / 95.5%
Study Inclusion Criteria – Attack Frequency	Run-in Period: ≥1 attack per 4 weeks	Historical: ≥2 attacks / month
Mean HAE Attacks/4 weeks	Last month prior to Screening: 3.90 During run-in: 3.66	During placebo treatment period: 4.24
Median (range) HAE Attacks/4 weeks	During Run-in: 3.0 (1.0, 14.7)	During placebo treatment period: 4.3 (2.0, 6.8)
Percentage of Subjects with ≥3 attacks per 4 weeks	52.0%	68.2%
History of Laryngeal attacks	64.8%	58.3%
Current use of LTP	56%; 48% used plasma-derived C1-INH	Not known
Source: DX-2930-03 CSR; LEVP 2005-1/B CSR		

The sponsor discussed the different studies in depth, highlighting similarities and differences that can affect comparability.

A comparison among these studies is difficult because the designs were different with respect to a number of factors including: the sequence of treatment (in parallel with placebo for Takhzyro and cross-over in the Cinryze and Berinert 2000/3000studies); the study duration (Takhzyro was the longest, with 26 weeks of observation); and the statistical analysis (the primary endpoint for lanadelumab was analysed with a generalized linear model for count data assuming a Poisson distribution with adjustment for baseline attack rate, while the primary endpoint for COMPACT study with BERINERT 2000/3000 was analysed using a mixed effects model assuming a continuous distribution). There were also 12 years between the Cinryze study and the ones of Berinert for prophylactic use (BERINERT 2000/3000) and Takhzyro.

Nonetheless some conclusions can be made, because all studies used the reduction in the frequency of attacks as the primary endpoint (although the definition of those endpoints has differed across studies), the secondary endpoints were also similar, and the study populations did not significantly differ with respect to the number of attacks as inclusion criteria (1 attack per month inclusion criterion), as shown in the table above.

The simple inter-trial comparison provided below in table 4, with all limitations described above, appears to suggest higher efficacy of Takhzyro and Berinert 2000/3000 as compared to Cinryze in the number of attacks (primary endpoint), severe breakthrough attacks, and number of responders. All endpoints performed better in the Berinert 2000/3000 and Takhzyro studies as compared to Cinryze. Similar efficacy of Berinert 2000/3000 and Takhzyro may be assumed from the table below.

Table 2.

	CINRYZE IV	BERINERT 2000/3000 SC[d]	Lanadelumab SC		
	1000 U IV q3-4 days N=22	60 IU/kg q3-4 days N=43	150 mg q4wks N=28	300 mg q4wks N=29	300 mg q2wks N=27
Treatment period	12 weeks	16 weeks (14wks efficacy measures; wk 3-16 of each study period)	26 weeks	26 weeks	26 weeks
Study design	Crossover	Crossover	Parallel-group		
Run-in period attack rate / month	NA	4	3.2	3.7	3.5
Primary endpoint[a]					
Treatment period mean attack rate/4 weeks Estimate (95% CI range)	2.1(1.50, 2.97)	0.52 (0.00, 1.04)	0.48 (0.31, 0.73)	0.53 (0.35, 0.77)	0.26 (0.14, 0.45)
Rate ratio (versus placebo) Estimate (95% CI range)	0.49 (0.36, 0.68)*	Not available	0.24 (0.15, 0.38)	0.26 (0.17, 0.40)	0.13 (0.07, 0.23)
Mean percent reduction in attacks versus placebo	50.3%* P<0.001	84% P<0.001	75.6% P<0.001	73.3% P<0.001	86.9% P<0.001
Other endpoints					
Responder analysis: subjects with attack reduction[b] ≥50% ≥70% ≥90%	50.0% 45.5% 18.2%	90% 83% 58%	89.3% 78.6% 64.3%	100% 75.9% 55.2%	100% 88.9% 66.7%
Attack-free subjects, %	18.2%	40%	39.3%	31.0%	44.4%
Reduction to <1 attack/4 weeks, %	45.5%	71%[c]	82.1%	82.8%	88.9%
Subjects with severe breakthrough attacks, %	31.8%	9%	17.9%	13.8%	7.4%

CI-confidence interval; IV=intravenous; q2wks=every 2 weeks; q3-4 days=every 3 to 4 days; q4wks=every 4 weeks; SC=subcutaneous; U=unit

[a] Model based estimates; The primary endpoint was analyzed using Poisson regression with adjustment for baseline attack rate for lanadelumab, and using a mixed effects model for BERINERT 2000/3000.

[b] Percentage reduction from placebo period for CINRYZE & BERINERT 2000/3000 and from run-in period for lanadelumab Source: Derived from LEVP 2005-1/B CSR (data on file) and Module 5.3.5.1, DX-2930-03 CSR, Section 11.2, Table 14.2.2.1

[c] Values are for patients who had at least one attack during a 4-week period while receiving placebo.

[d] Longhurst et al. 2017. HAEGARDA has been registered as BERINERT 2000/3000 in the UK and Germany.

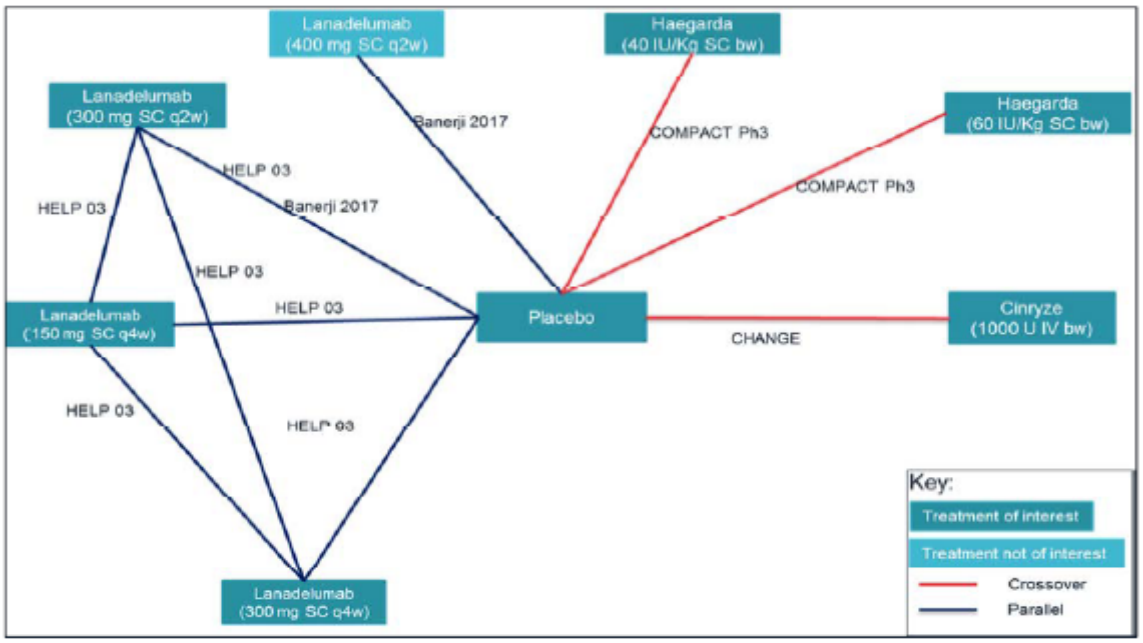
* Rate ratio and percent reduction are from generalized estimating equation (GEE) modeling.

The sponsor performed also an indirect comparison. A Bayesian network meta-analysis was used to compare time to first attack after Day 0, Day 14 and Day 70 with data from the HELP study (SC Takhzyro 300 mg q2wks, 300 mg q4wks, 150 mg q4wks versus placebo; 26-weeks treatment period), the CHANGE study (IV C1-INH 1000U q3-4 days for 12 weeks, crossover to placebo for 12 weeks) and COMPACT study (HAEGARDA 40IU/kg SC bi-weekly, HAEGARDA 60IU/kg SC bi-weekly incomplete crossover to; 16 weeks) (Note: as previously mentioned, Haegarda is the commercial name of Berinert 2000/3000 in the US).

The proportion of attack-free patients was estimated for up to 60 months by (1) fitting parametric survival models (PSM) to time to first attack in the HELP lanadelumab and placebo arms; (2) calculating hazard ratios (HRs) from fitted PSMs; and (3) combining HRs and PSMs for time to first attack in the placebo arm of HELP to predict the survival curve for IV C1-INH and HAEGARDA. Figure 1 shows the final network analysis performed by the sponsor. The figure contains the study mentioned above that were the final studies used for the indirect treatment comparison (ITC) once all available

trials were screened and critically appraised (the methodology for such critical appraisal is described by the sponsor at annex 4 and appears acceptable).

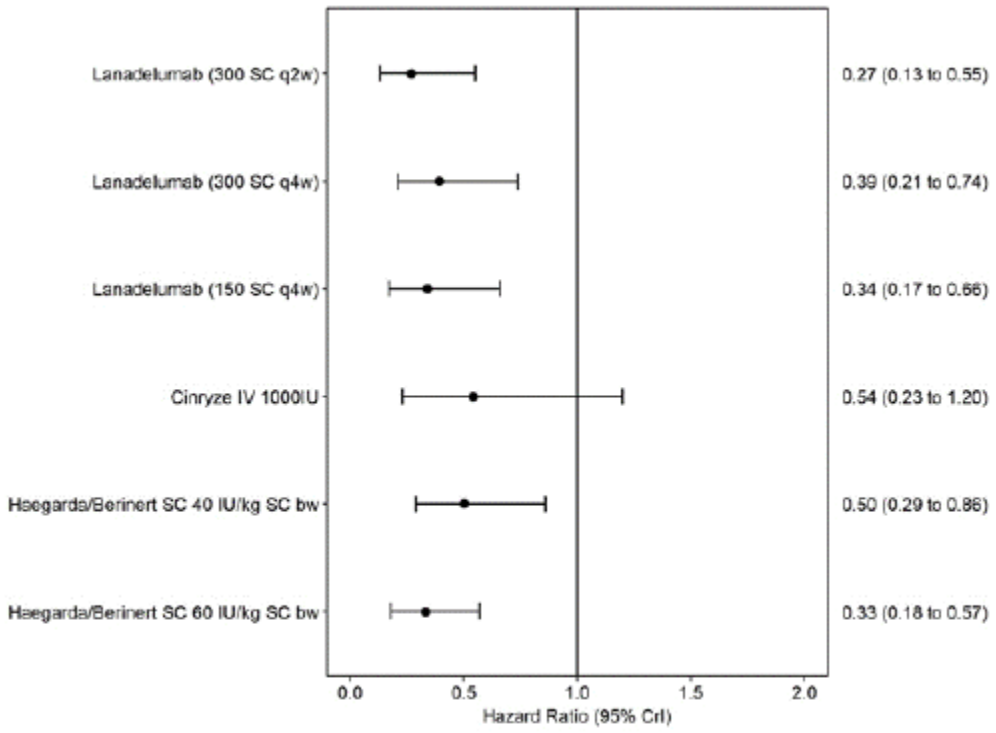
Figure 1. final network diagram for ITC



Key: SC, subcutaneous; IV, intravenous; IU, international unit; Ph3, phase 3; q2w, every 2 weeks; q4w, every 4 weeks; bw, weekly

The results showed a comparable efficacy between Takhzyro and Berinert 2000/3000 (EU commercial name of Haegarda) on time to first attack after Day 0 (figure 2). More in detail, the reduction in risk of experiencing a first attack for patients receiving HAEGARDA 60IU/kg compared to placebo was similar to the reduction for patients receiving Takhzyro 300 mg q4wks (HR= 0.33, 95% CrI 0.18 to 0.58).

Figure 2. Fixed Effect Model: Hazard Ratio of Treatment Versus Placebo (After Day 0)

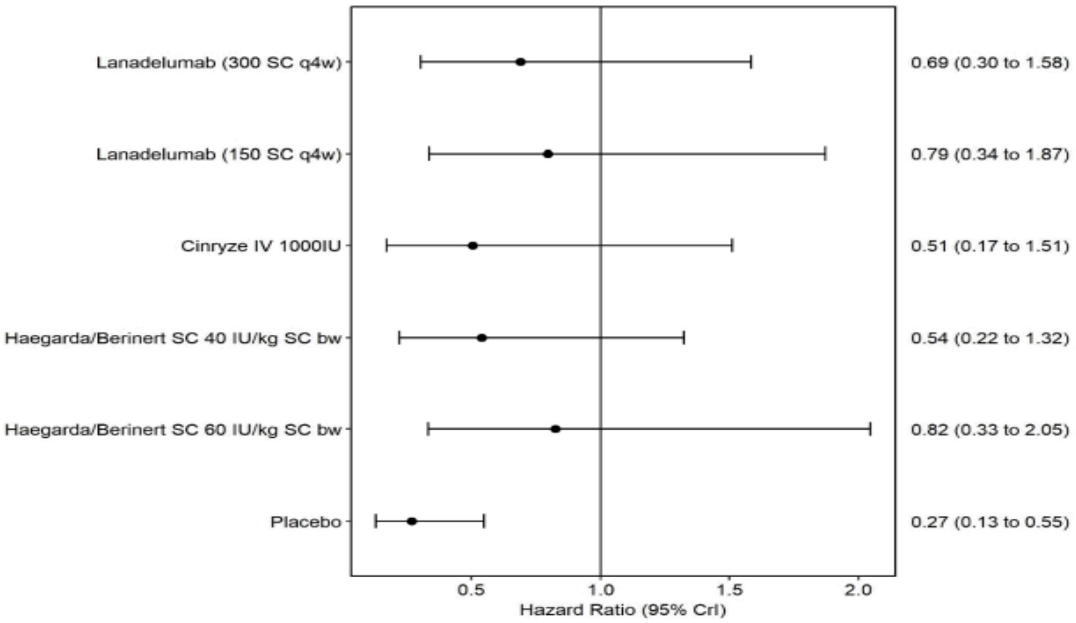


q2w=every 2 weeks; q4wks=every 4 weeks

The results of the comparison of attacks after day 14 and day 70 went in the same direction. The sponsor states that compared to the results from the analysis of the time to first attack after Day 14, the predicted median hazard ratios after Day 70 for each lanadelumab dose are smaller in the network meta-analysis (NMA) for time to first attack.

The comparison of each of the other treatments with each lanadelumab (Takhzyro) dose was presented by the sponsor by forest plots of lanadelumab 150mg q4w versus all other treatments, lanadelumab 300mg q4w versus all other treatments, and lanadelumab 300mg q2w versus all other treatments. A median hazard ratio less than 1 in these forest plots means that Lanadelumab 150mg q4w, 300mg q4w and 300mg q2w respectively reduces the risk of experiencing a first attack compared to the other treatments. Figure 3 below shows the forest plot of the hazard ratio of Lanadelumab 300 mg q2w, versus Cinryze and Haegarda

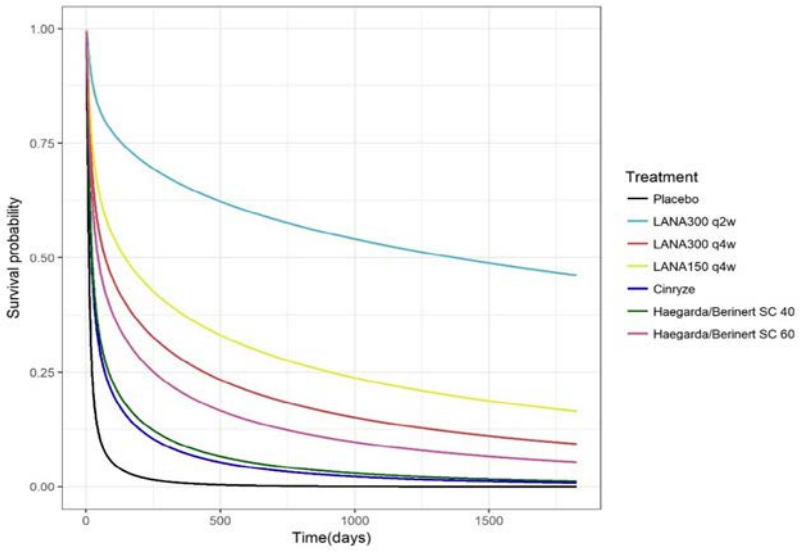
Figure 3. Forest plot of the hazard ratio of Lanadelumab 300 mg q2w, versus Cinryze and Haegarda (the name under which Berinert for subcutaneous administration is marketed in US, corresponding to Berinert 2000/3000 in the EU).



The sponsor discussed with the COMP the indirect comparison of Takhzyro with Berinert 2000/3000 (the subcutaneous formulation of Berinert), claiming lower attack rate with Takhzyro at steady state (estimated at 16 weeks for Takhzyro and at 14 weeks for Berinert in the respective studies). The mean reduction of attack rate was 91% for Takhzyro and 84% for Berinert and the percentage of attack free patients was 77% and 40%, respectively. However there was no statistically significant difference in the calculations provided with the indirect comparison. In addition the COMP noted, as also highlighted by the applicant in their submission, that there are several limitations in the comparability of the pivotal clinical trial of Takhzyro with the Berinert 2000/3000 trial. This includes some differences in attacks of angioedema in the 3 months before screening (10.5 attack in Takhzyro trial and 9.8 in the Berinert trial) although the number of attacks in the run-in period was comparable (3.7 and 4 attacks /month, respectively)."

Predicted survival curves were also derived by the sponsor for each treatment (lanadelumab, CINRYZE, and HAEGARDA), for each of the three endpoints time to first attack after Day 0, 14 and 70, by combining the hazard ratios from the ITCs and the spline survival curve fitted to the Study DX-2930-03 placebo data. The most relevant findings from these curves are that lanadelumab (300 mg q2wks) presents the numerically greatest predicted proportion of attack-free patients over all time points. After 60 months, the predicted proportion of attack-free patients taking lanadelumab (300 mg q2wks) is 0.462 but for CINRYZE the proportion is only 0.008. Figure 4 below presents the predicted survival curve of the time to first attack after Day 70 for each lanadelumab dose, HAEGARDA 40IU/kg, HAEGARDA 60II/kg, and CINRYZE. The curves plotted closest to the survival probability of 1 are predicting a higher proportion of patients that are attack-free attack time point and therefore a higher time to first attack.

Figure 4. Predicted Survival Curves: Time to First Attack After Day 70



Conclusions on improved efficacy

From the data presented by the sponsor it would appear that Takhzyro provides better efficacy than Cinryze on protection for HAE attacks as well on other aspects (e.g. attack severity). The differences between Cinryze and Takhzyro appear numerically and clinically relevant although it would appear that there is not statistical significance of the differences. A key limitation of efficacy comparison between those two products was that extrapolation was based on short observation periods, as previously discussed, due to the differences in study duration of the studies. However, the methodology of the indirect comparison was extensively discussed by the sponsor and the uncertainty around a number of assumptions was justified.

Regarding Berinert 2000/3000 the results of indirect comparison suggest an overall comparable reduction in attack rates with lanadelumab. Modelling of the available clinical trials data of Takhzyro and Berinert showed that after 5 years, 46% of patients treated with lanadelumab 300 mg q2wks would be attack-free, versus 5% with Berinert SC 60 IU/kg (q3-4days). However, the time to first attack after day 0 for patients treated with lanadelumab v was not significantly different than Berinert . Based on the model, the risk of first attack after day 70 was significantly lower for patients treated with lanadelumab. Extrapolation based on these results showed that after 5 years, 46% of patients treated with lanadelumab 300 mg q2wks would be attack-free, versus 5% with Berinert 2000/3000 (q3-4days).

The indirect comparison on the other hand showed a clear clinical advantage of Takhzyro compared to Cinryze, including clinically relevant differences in attack rates and time to first attack after Day 0.

The COMP concluded that in view of the majority of the results showing comparable efficacy of Takhzyro to Berinert, with only the simulated attack-free rate at 5 years showing a difference, a claim of better efficacy of Takhzyro than Berinert could not be accepted, and the two products can be considered to have comparable efficacy based on the data available at the time of this assessment. Takhzyro was considered to have better efficacy than Cinryze.

Major contribution to patient care

The sponsor proposes differences in the dosing schedule as the main ground for significant benefit based on major contribution to patient care.

Takhzyro has a long half-life (14 days) allowing a once or twice monthly subcutaneous administration therefore the sponsor argues that the burden of treatment is significantly lower than that of the

currently authorized main comparators (for the same prophylactic indications) Cinryze and Berinert. In the agreed SmPC the recommended starting dose is 300 mg lanadelumab every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered, especially in patients with low weight.

Cinryze requires IV administration every 3 or 4 days and a major contribution to patient care of Tahkzyro may be assumed, as such frequent IV administration usually requires the placement of a permanent venous access or repeated IV injections. A significant benefit of Takhzyro vs Cinryze may be based on ease of use linked to administration route and the dosing schedule.

Regarding Berinert2000/3000, the administration route is the same (subcutaneous) as Takhzyro but Berinert2000/3000 requires administration every 3-4 days, and reconstitution with a large volume of water per reconstituted vial (4 mL to 6 mL) compared to 2 mL of Takhzyro subcutaneously every 2 or 4 weeks.

The sponsor supported the application also with an analysis of quality of life data. Patients treated with TAKHZYRO observed a statistically significant improvement in HRQoL as measured by the AE-QoL during the 26-week treatment period (Day 0 to Day 182), with statistically significant and clinically meaningful improvement in AEQoL total score and all domain (functioning, fatigue/mood, fear/shame, and nutrition) compared to placebo. The largest improvement was observed in the functioning domain. Table 5 shows the overall AE-QoL score of treatment versus placebo.

Table 3. Change in AE-Qol Scores for TAKHZYRO† Versus Placebo (ITT Population)

Treatment Arms	AE-QoL Least Squares Mean Change (SD)‡				
	Total	Functioning	Fatigue/Mood	Fear/Shame	Nutrition
Placebo	-4.7 (18.6)	-5.4 (22.9)	-1.8 (23.2)	-9.1 (23.9)	0.5 (22.4)
TAKHZYRO†	-19.5 (18.6)**	-29.3 (22.9)**	-13.0 (23.1)*	-18.8 (23.7)**	-17.0 (22.3)**

Notes: AE-QoL= Angioedema Quality of Life Questionnaire; ITT=intent-to-treat; SD= standard deviation

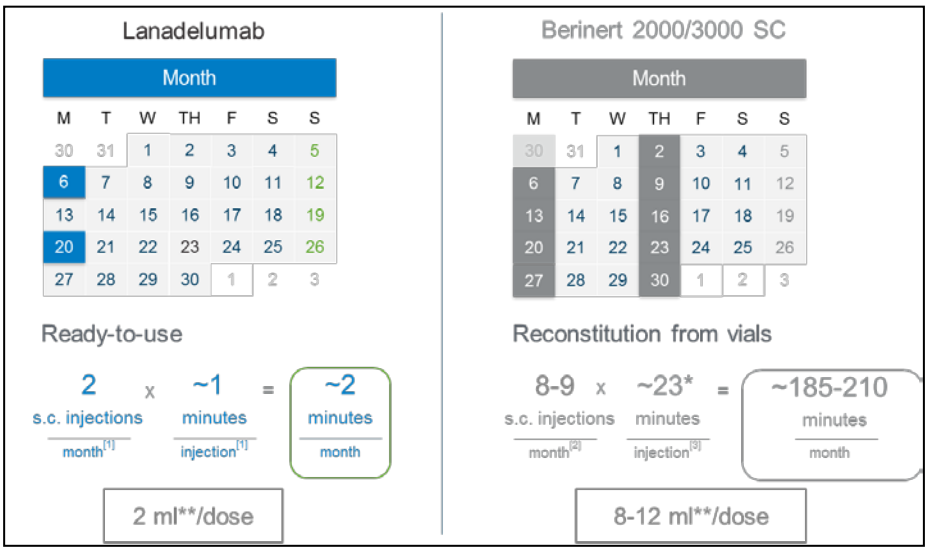
† TAKHZYRO combines data from all 3 TAKHZYRO treatment arms (150 mg q4wks, 300 mg q4wks, and 300 mg q2wks).

‡ Comparison between TAKHZYRO and placebo arms for change in AE-QoL total and domain scores from Day 0 to Day 182 were conducted using analysis of covariance (ANCOVA), adjusting for baseline scores.*p-value=0.01; **p-value<0.01

The sponsor also presented and discussed quality of life data comparing Takhzyro (HELP study) with studies with a proprietary C1-INH for subcutaneous use (C1-INH SC) at the stage of investigational agent, at the same dosing schedule as the authorized Berinert 2000/3000. The AE-QoL (angioedema quality of life questionnaire) was used to measure disease-specific quality of life. The data showed higher rate of responders (defined as reduction of at least 6 points in AE-QoL total score) with lanadelumab 300 mg every 2 weeks with an odds ratio versus placebo of 7.2. The results were considered relevant by the COMP although the statistical significance of the difference in responders could not be established.

From the point of view of convenience of use, the 2 times a month administration schedule of lanadelumab was compared by the sponsor to the authorized dosing schedule of Berinert 2000/3000 (every 3 or 4 days), taking into account also the volume that needs to be administered subcutaneously at each injection, i.e. 2 ml/dose for Takhzyro and 8-12 ml/dose for Berinert 2000/3000 (figure 5).

Figure 5. From Banerji et al (2018), Longhurst et al. (2017) and Murphy et al. (2018)



*15-30 minutes
**volume for 60-100 kg per injection/infusion

Conclusion on major contribution to patient care

The COMP discussed the reduction of treatment burden linked to the lighter dosing schedule of Takhzyro and its impact on patients, and considered that it could be considered sufficiently relevant to be granted a significant benefit based on major contribution to patient care. Takhzyro can be administered subcutaneously at 300 mg every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg every 4 weeks may be considered, especially in patients with low weight. Cynrize has an intravenous administration route, requiring administration every 3 or 4 days. A major contribution to patient care of Tahkzyro can be assumed, as such frequent IV administration usually requires the placement of a permanent venous access or repeated IV injections. Regarding Berinert 2000/3000, the administration route is the same (subcutaneous) but Berinert 2000/3000 requires administration every 3-4 days, and reconstitution with a large volume of water per reconstituted vial (4 mL to 6 mL), compared to 2 mL of Takhzyro subcutaneously every 2 or 4 weeks. The COMP considered that the less frequent dosing schedule represents a major contribution to patient care. The quality of life data presented by the sponsor were considered relevant as supportive evidence but did not constitute the main ground for a major contribution to patient care.

The committee expressed a positive opinion on the maintenance of the orphan status based on major contribution to patient care, with three members signing a divergent opinion.

COMP position adopted on 26 October 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.
- the prevalence of hereditary angioedema (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded less than 0.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the COMP considered that Takhzyro is of significant benefit to those affected by the orphan condition. Based on an indirect comparison, Takhzyro showed better results in preventing angioedema attacks than the C1 inhibitor Cinryze, currently authorized for the condition. Takzyro showed similar efficacy as Berinert 2000/3000, another C1 inhibitor also authorized for the condition. In relation to the recently approved subcutaneous formulation of Berinert 2000/3000, Takhzyro has a more favourable dosing schedule and more convenient administration, which allows treatment every two weeks instead of every 3 to 4 days. The Committee considered that this is a major contribution to patient care as it reduces the treatment burden for the patients affected by the condition.

the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Takhzyro, recombinant human IgG1 kappa light chain monoclonal antibody targeting plasma kallikrein, lanadelumab, EU/3/15/1551 for treatment of hereditary angioedema is not removed from the Community Register of Orphan Medicinal Products.

Divergent position expressed by some members of the COMP

Efficacy and safety of lanadelumab is in the same range as comparators licensed for the same indication. Therefore, significant benefit cannot be based on improved efficacy, but must be based on a major contribution to patients care.

The applicant failed to show convincing data proving that the more convenient mode of administration actually translates into relevant improvement of quality of life.

Therefore, the COMP members below are of the opinion, that the provided data are not enough to support maintenance of orphan status.

Austria	Brigitte Blöchl-Daum
Denmark	Elisabeth Penninga
Spain	Fernando Mendez Hermida