25 March 2021
EMA/233643/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

TAKHZYRO

lanadelumab

Procedure no: EMEA/H/C/004806/P46/001.1

Note

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

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1. Introduction

On 9 April 2020, the MAH submitted a completed paediatric study for Takhzyro, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study DX-2930-04 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

For each 300mg dose of lanadelumab, each subject received a total of 2 vials, each containing a nominal concentration of 150mg of lanadelumab active ingredient in 1mL solution. When Takhzyro became available, subjects transitioned to a single vial of 2mL solution (first subject transitioned on 02 Aug 2018).

2.3. Clinical aspects

2.3.1. Introduction

Lanadelumab is a fully human, monoclonal antibody specifically inhibiting of active plasma kallikrein (pKal) activity.

Plasma kallikrein is established as a relevant target for hereditary angioedema (HAE). In HAE, pKal activity is dysregulated due to the absence of C1-inhibitor (C1-INH), which results in the release of excess amounts of bradykinin. Bradykinin is a vasodilator responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain.

Lanadelumab (marketed as Takhzyro) is approved in a total of 40 countries globally including the United States, Canada, and the European Union (in 2018) for routine prophylaxis to prevent attacks of HAE in patients 12 years and older.

In procedure EMEA/H/C/004806/P46/001, the MAH submitted a final report for:

- ***Study DX-2930-04****: HELP Study Extension: An Open-Label Study to Evaluate the Long-Term Safety and Efficacy of DX-2930 for Prevention Against Acute Attacks of Hereditary Angioedema (HAE)*

Study DX-2930-04 was part of the agreed paediatric investigational plan (PIP). Therefore, the current submission includes data from the aforementioned study, which has been completed in the last 6 months, in order to comply with the requirements stipulated in Article 46 of the Paediatric Legislation (Regulation 1901/2006, as amended).

Study DX-2930-04 is also listed as an additional pharmacovigilance activity category 3 PASS in the Takhzyro RMP.

The current procedure assesses the MAH's Responses to the questions included in the CHMP Assessment Report for Takhzyro Art. 46 procedure related to study DX-2930-04 (EMEA/H/C/004806/P46/001).

2.3.2. Clinical study

A summary of the assessment of study DX-2930-04 in procedure EMEA/H/C/004806/P46/001 is presented here. For details, please refer to the Assessment Report for procedure EMEA/H/C/004806/P46/001.

Efficacy

Study DX-2930-04 was an open-label, long-term safety, and efficacy multicentre extension study of the pivotal study DX-2930-03 conducted in the US and Europe. Two types of subjects were enrolled into this study: rollovers from Study DX-2930-03 and non-rollovers (i.e., were not participants in Study DX-2930-03). There were no primary efficacy endpoints in the study. An interim analysis covering the first six months of Study DX-2930-04 was submitted and assessed in the MAA for Takhzyro.

A total of 212 subjects were treated in the study, including 109 subjects that rolled over from DX-2930-03 and 103 non-rollover subjects. Among them, 21 adolescent subjects (including 8 rollovers) were exposed to lanadelumab in Study DX-2930-04.

For rollover patients treated with placebo in pivotal study DX-2930-03, there was a marked decrease in median HAE attack rate from 1.82 attacks/month at the end of the DX-2930-03 treatment period to 0.06 attacks/month in the end of study DX-2930-04. This decrease in attack rate was consistent with the decrease in attack rate in the lanadelumab subjects during study DX-2930-03. The decrease in attack rate in the rollover lanadelumab subjects was maintained through study DX-2930-04. For the non-rollover subjects, data are presented by prior treatment (no long-term prophylaxis [LTP], LTP with C1-inhibitors [C1-INH], LTP with oral therapy or LTP with both C1-INH and oral therapy). The number of subjects in the two latter groups was small: N=9 and N=2, respectively. Regardless of prior treatment there was a marked decrease in attack rate from 1.54-1.84 attacks/month at baseline to 0.00-0,15 attacks/month at the end of study DX-2930-04.

The timeline for lanadelumab efficacy was also provided. The mean attack rate in the non-rollover population decreased from 2.55 attacks/month at baseline to 0.35 attacks/month after one month of treatment. At Month 30, the median HAE attack rate was 0.00 (min, max: 0.00, 2.9) in both populations. The mean (SD) HAE attack rate for the rollover population was 0.18 (0.55) and for the non-rollover population 0.19 (0.49). The number of subjects with data at Month 30 were 71/109 (65%) and 82/103 (80%) for rollovers and non-rollovers, respectively. As mentioned elsewhere, the most common reason for discontinuing treatment was transition to commercial lanadelumab outside the study.
Taken together these data confirm the results from pivotal study DX-2930-03 and support long term efficacy of lanadelumab.

Demographic background, medical history and efficacy outcome were not presented separately for the 21 paediatric subjects in the paediatric population. As the study is part of the PIP, the MAH was asked to present main data (discontinuation rate, demographics and baseline conditions, and mean HAE attack rate) for the paediatric population, the adult population and the total population separately, preferably in a comprehensive table.

Self-administration of Takhzyro was allowed during the study; both at home and at a health care setting. The majority of the doses in the study were self-administered. 32% of all doses were self-administered at home. This did not affect the effect on mean HAE attack rates.

A secondary efficacy endpoint was patient-reported assessments of quality of life with the established AE-QoL assessment tool. The change observed in the AE-QoL total score was well over 6, which is the

minimal clinically important difference (MCID) reported in the literature, in the patients not previously treated with lanadelumab. Self-reported symptom scales should be assessed with great caution in open label studies. Notwithstanding, the results are compatible with the improvements in HAE attack rate.

Safety

There were no deaths reported during the study.

TEAE, SAE and discontinuations

Any TEAE excluding HAE attack (non-HAE TEAE) was reported by 97% of the subjects overall, with no clinically relevant difference between rollovers and non-rollovers. In DX-2930-03, overall, 90% of the subjects reported any non-HAE TEAE. The proportion of subjects with non-HAE TEAE in DX-2930-04 was however comparable to that in the 300 mg q2w arm of DX-2930-03 (97% and 96%, respectively).

No separate information on TEAE in the paediatric population is given. The MAH was asked to provide a table similar to the table "Summary of Treatment-emergent Adverse Events Excluding HAE Attack Reported Events During the Treatment Period") for subjects <18 years, ≥18 years and the total population separately.

The most commonly reported non-HAE TEAE by preferred term in both DX-2930-04 and DX-2930-03 were injections site pain (47%, 52% and 43% for DX-2930-04, DX-2930-03 300mg q2w population and DX-2930-03 total population, respectively), followed by viral upper respiratory tract infection (42%, 37%, 24%), upper respiratory tract infection (26%, NA, NA) and headache (24%, 33%, 20%). Headache is further discussed below.

A total of 116 (55%) subjects had 2,120 related non-HAE TEAEs. The vast majority of related non-HAE TEAEs were reported in the SOC General disorders and administration site conditions (2,090/2,120 events). Of these, all but seven events represented different forms of injection site reactions. The proportion of subjects with related non-HAE TEAE in DX-2930-03 was 60% in the overall study population and 70% in the 300 mg q2w arm.

The paediatric population comprises 10% of the total study population (21/212 subjects). Of the 2,120 reported related non-HAE TEAE, 251 events (6%) were reported in the paediatric population. Thus, there are no indications that adverse events related to lanadelumab treatment were more common in this population. 250/251 events in the paediatric population represented injection site reactions.

A total of 21 subjects (9.9%) had 31 serious non-HAE TEAE. None of the serious TEAEs were assessed by investigators as related to lanadelumab. At preferred term (PT)-level, most SAEs were reported only for one single subject. Even though a causal association is often difficult to fully exclude, such an association is considered less probable in most of the cases, as other explications were more plausible. In summary, the list of SAEs in study DX-2930-04 does not indicate any new and unexpected safety risk with lanadelumab.

Six subjects discontinued from the study due to TEAEs. The events leading to discontinuation were hypersensitivity (3), elevated liver enzymes (2) and upper gastrointestinal bleeding following ingestion of a caustic substance. The events of hypersensitivity were assessed as related to lanadelumab by the Investigator. This is agreed; however, elevated liver enzymes are labelled in section 4.8 and a causal association is therefore at least possible in one of the cases. In the other case, the elevated liver enzymes were reported just prior to the first lanadelumab dose.

Specific issues

Based on both the known safety profile of lanadelumab, missing safety information and a safety signal, the following adverse events are discussed in greater detail below: Injection site reactions, headache, pregnancy, hypersensitivity, disordered coagulation, elevated liver enzymes and immunogenicity.

In total, 55% of the subjects in DX-2930-04 reported at least one TEAE of injection site reaction. No events were serious, and none led to discontinuation. Injection site reactions are labelled with the frequency "very common" in section 4.8.

During the reporting period for the second six-month PSUSA for lanadelumab (23 February 2019 to 22 August 2019; EMEA/H/C/PSUSA/00010743/201908), a safety signal of headache was identified by the MAH. The MAH reviewed, refuted and closed the signal with no proposed changes to the SmPC. The PRAC agreed that based on the non-serious nature of the headache cases, it was sufficient to closely monitor the signal of headache. The MAH was also to provide a cumulative analysis of clinical trial data through data base lock of 19 December 2019 in DX-2930-04 study and post-marketing data of headache for current interval period (23 August 2019 to 22 February 2020) in the third six-month PSUSA (EMEA/H/C/PSUSA/00010743/202002). No additional measures were undertaken based on data presented in the PSUSA dated 202002. However, the PRAC Rapporteur, stated that "Reassessment of the signal of headache is expected after the end of the open label extension study".

Overall, 118 subjects reported 120 events of headache including related PTs as adverse events in DX-2930-04. 78% of the events were reported more than three days after the injection. The same information was presented also in the PSUSA 202002. Thus, no additional data on headache has emerged from Study DX-2930-04 compared to the cumulative review assessed in procedure EMEA/H/C/PSUSA/00010743/202002. No post-marketing data has been provided with the current procedure. As no new information is available in this current procedure, there is no ground to reconsider the recommendation in procedure EMEA/H/C/PSUSA/00010743/202002, that no new safety related updates to the product information related to headache is warranted. It is considered adequate to continue monitoring headache by routine pharmacovigilance and in upcoming PSUSAs.

The results from study DX-2930-04 do not warrant any update of the current wording of section 4.6 of the approved Takhzyro SmPC.

No anaphylaxis and no anaphylactoid reactions were observed during the study. The risk of Hypersensitivity is reflected in sections 4.4 and 4.8 of the SmPC.

At the MAA of Takhzyro, it was noted that in study DX-2930-03, activated partial thromboplastin time (aPTT) was well balanced between groups at baseline. However, a dose-dependent increase in aPTT appeared from the first measurement after study start, i.e. day 28. These changes were then maintained throughout the study period up to day 182. The changes from baseline were in line with what can be predicted from primary pharmacology and were considered to be due to an interaction of lanadelumab with the aPTT assay. This is reflected in section 4.4 of the SmPC.
All bleeding events except two were reported in one single subject. Vaginal bleeding was reported in two subjects, however, was associated with adenomyosis in one of the subjects. Six episodes of epistaxis were reported, all in the same subject. Nevertheless, the MAH was asked to provide a comprehensive summary, preferably as a table, of bleeding parameters at the time for the event, including aPTT, in all subjects reporting a bleeding event.

Three events associated with thromboembolic events were reported (thrombosis, Transient ischaemic attack and Cerebrovascular Accident). After assessing the narratives, it is agreed with the MAH that in none of the SAE associated with thromboembolic events, a causal association to lanadelumab treatment is considered probable.

Shift from normal liver enzyme levels at baseline to 1 to <3×ULN was reported in 25% of the patients for ALT and 22% of the subjects for AST. Seven subjects (3.3%) had at least one ALT value >3 x ULN. The same number of subjects had at least one AST value >3 x ULN. No subjects met the criteria for the Hy's law cases.
Five subjects had liver-related test results that led to interruption (n=2) or withdrawal of lanadelumab treatment (n=3). The remaining subjects with elevated liver enzymes continued treatment with lanadelumab.
Alanine aminotransferase increased and Aspartate aminotransferase increased are labelled in section 4.8 with frequency common. This is considered adequate.

During Study DX-2930-04, six subjects developed neutralising anti-drug antibodies (ADAs) at least at one timepoint. After having assessed the narratives for these six subjects as summarised above, it is agreed with the MAH, that this does not seem to have had any impact on the efficacy of lanadelumab. One of the six subjects with neutralising antibodies was a boy. This was the only subject from the paediatric population reporting neutralising antibodies.

2.3.3. Assessment of the MAH's responses to the question in procedure EMEA/H/C/004806/P46/001

Question 1

Demographic background, medical history and efficacy outcome were not presented separately for the 21 paediatric subjects in the paediatric population. As Study DX-2930-04 is part of the PIP, the MAH is asked to present main data (discontinuation rate, demographics and baseline conditions, and mean HAE attack rate) for the paediatric population, the adult population and the total population separately, preferably in a comprehensive table

Summary of the MAH's response

Subject disposition, demographics, baseline characteristics and mean HAE attack rate are presented in Table 1, Table 2, Table 3, Table 4 and Table 5 below for the paediatric, adult, and total populations separately.

Table 1: Subject Disposition (Safety Population)

	Subjects < 18 years[a] N = 21	Subjects ≥ 18 years[a] N = 191	Total Population[b] N = 212
Number of subjects treated	21 (100.0)	191 (100.0)	212 (100.0)
Completed study	8 (38.1)	48 (25.1)	56 (26.4)
Completed study or transitioned to commercial product	20 (95.2)	153 (80.1)	173 (81.6)
Completed at least 30 months	20 (95.2)	153 (80.1)	173 (81.6)
Did not complete study	13 (61.9)	143 (74.9)	156 (73.6)
Primary reason for study withdrawal			
Adverse event	0 (0.0)	6 (3.1)	6 (2.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (4.8)	1 (0.5)	2 (0.9)
Physician decision	0 (0.0)	3 (1.6)	3 (1.4)
Pregnancy	0 (0.0)	4 (2.1)	4 (1.9)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal by subject	12 (57.1)	126 (66.0)	138 (65.1)
Transitioned to commercial product	12 (57.1)	105 (55.0)	117 (55.2)
Other	0 (0.0)	21 (11.0)	21 (9.9)
Other	0 (0.0)	3 (1.6)	3 (1.4)

Note: There were 2 subjects who completed the study under Protocol Amendment 2 of the protocol and re-entered the study under Protocol Amendment 3. Percentages are based on the safety population. The rollover safety population included all subjects in the safety population who participated in the DX-2930-03 study. The nonrollover safety population included all subjects in the safety population who enrolled in DX-2930-04 study directly.

Table 2: Demographic Characteristics (Safety Population)

Characteristics	Subjects < 18 years[a] N = 21	Subjects ≥ 18 years[a] N = 191	Total Population[b] N = 212
Age (years)			
n	21	191	212
Mean (SD)	14.3 (1.61)	43.6 (13.74)	40.7 (15.73)
Median	14.2	44.7	42.8
Min, max	12, 18	18, 76	12, 76
Age category, n (%)			
<18 years	21 (100.0)	0	21 (9.9)
18 to <40 years	0	77 (40.3)	77 (36.3)
40 to <65 years	0	103 (53.9)	103 (48.6)
≥65 years	0	11 (5.8)	11 (5.2)
Sex, n (%)			
Male	11 (52.4)	58 (30.4)	69 (32.5)
Female	10 (47.6)	133 (69.6)	143 (67.5)
Ethnicity, n (%)			
Hispanic or Latino	1 (4.8)	12 (6.3)	13 (6.1)
Not Hispanic or Latino	20 (95.2)	178 (93.2)	198 (93.4)
Unknown	0	1 (0.5)	1 (0.5)
Race, n (%)			
White	20 (95.2)	178 (93.2)	198 (93.4)
Black or African American	1 (4.8)	9 (94.7)	10 (4.7)
Native Hawaiian or Other Pacific Islander	0	0	0 (0.0)
Asian	0	2 (1.0)	2 (0.9)
American Indian or Alaska Native	0	0	0 (0.0)
Multiple	0	1 (0.5)	1 (0.5)
Other	0	1 (0.5)	1 (0.5)
Race group, n (%)			
White	20 (95.2)	178 (93.2)	198 (93.4)
Non-white	1 (4.8)	13 (6.8)	14 (6.6)

max=maximum, min=minimum, SD=standard deviation
Note: Age calculated as the difference between date of birth and date of informed consent, truncated to years.

Table 3: Baseline Characteristics (Weight and BMI) (Safety Population)

Characteristics	Subjects < 18 years[b] N = 21	Subjects ≥ 18 years[b] N = 191	Total Population[c] N = 212
Weight (kg)			
n	21	191	212
Mean (SD)	66.8 (24.45)	82.1 (23.08)	80.60 (23.609)
Median	62.1	77.3	75.60
Min, max	37, 127	48, 178	36.7, 177.7
Weight category, n (%)			
<50 kg	5 (23.8)	2 (1.0)	7 (3.3)
50 to <75 kg	12 (57.1)	83 (43.5)	95 (44.8)
75 to <100 kg	1 (4.8)	70 (36.6)	71 (33.5)
≥100 kg	3 (14.3)	36 (18.8)	39 (18.4)
BMI (kg/m^2)[a]			
n	21	191	212
Mean (SD)	25.2 (7.14)	28.7 (7.09)	28.35 (7.161)
Median	23.9	27.2	26.93
Min, max	17, 40	17, 55	16.9, 55.0

BMI=body mass index; max=maximum, min=minimum, SD=standard deviation

[a] BMI calculated as [weight (kg)/height $(m)^2$]. BMI was derived by study staff at the site.

Table 4: Baseline HAE Attack Characteristics (Safety Population)

Characteristics	Subjects < 18 years[c] N = 21	Subjects ≥ 18 years[c] N = 191	Total Population[d] N = 212
Age at onset of angioedema symptoms (years)			
n	21	191	212
Mean (SD)	7.0 (3.47)	13.2 (8.72)	12.6 (8.55)
Median	7.0	13.0	12.0
Min, max	1, 13	1, 49	1, 49
HAE type, n (%)			
Type I	18 (85.7)	171 (89.5)	189 (89.2)
Type II	3 (14.3)	18 (9.4)	21 (9.9)
Unspecified	0	2 (1.0)	2 (0.9)
History of laryngeal attacks, n (%)			
Yes	8 (38.1)	122 (63.9)	130 (61.3)
No	13 (61.9)	69 (36.1)	82 (38.7)
Primary attack locations (combined), n (%)[a]			
Laryngeal	5 (23.8)	39 (20.4)	44 (20.8)
Abdominal	17 (81.0)	164 (85.9)	181 (85.4)
Peripheral	19 (90.5)	153 (80.1)	172 (81.1)
Primary attack locations, n (%)			
Laryngeal	0	0	0 (0.0)
Laryngeal/abdominal	0	5 (2.6)	5 (2.4)
Laryngeal/peripheral	2 (9.5)	4 (2.1)	6 (2.8)
Laryngeal/abdominal/peripheral	3 (14.3)	30 (15.7)	33 (15.6)
Abdominal	2 (9.5)	33 (17.3)	35 (16.5)
Abdominal/peripheral	12 (57.1)	96 (50.3)	108 (50.9)
Peripheral	2 (9.5)	23 (12.0)	25 (11.8)
Historical number of attacks in the last month			
Mean (SD)	1.8 (1.63)	3.5 (3.73)	3.4 (3.61)
Median	1.0	2.0	2.0
Min, max	0, 6	0, 30	0, 30
Historical number of attacks in the last 3 months			
Mean (SD)	4.9 (4.52)	9.9 (10.96)	9.4 (10.60)
Median	4.0	6.0	6.0
Min, max	1, 20	0, 90	0, 90
Historical number of attacks in the last 12 months			
Mean (SD)	20.2 (18.43)	35.7 (42.22)	34.2 (40.73)
Median	12.0	24.0	22.0
Min, max	1, 80	0, 365	0, 365
Baseline HAE attack rate (attacks/4 weeks)[b]			
Mean (SD)	1.6 (1.02)	3.2 (2.73)	3.05 (2.657)
Median	1.2	2.5	2.00
Min, max	0, 4	0, 15	0.0, 15.4
Baseline HAE attack rate group[b] (attacks/4 weeks), n (%)			
<1	3 (14.3)	22 (11.5)	25 (11.8)
1 to <2	13 (61.9)	61 (31.9)	74 (34.9)
2 to <3	3 (14.3)	27 (14.1)	30 (14.2)
≥3	2 (9.5)	81 (42.4)	83 (39.2)

HAE=hereditary angioedema, max=maximum, min=minimum, SD=standard deviation

[a] Subjects may have been counted in more than 1 category.

[b] The baseline HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the run-in period of Study DX-2930-03 for rollover subjects or the number of HAE attacks during the historical reporting period for nonrollover subjects divided by the number of days the subject contributed to the run-in period for rollover subjects or historical reporting period for nonrollover subjects multiplied by 28 days. For nonrollover subjects, the historical rate in the last 3 months prior to screening was used.

[c] Source: [redacted]

[d] Source: [redacted]

The safety population included all subjects who received study drug. The rollover safety population included all subjects in the safety population who participated in DX-2930-03 study. The nonrollover safety population included all subjects in the safety population who enrolled in DX-2930-04 directly.

Table 5: Mean HAE Attack Rates

Subjects < 18 years[f]			Subjects ≥ 18 years[f]			Total Population[g]		
Rollover Subjects N=8	Non-Rollover Subjects N=13	Total N=21	Rollover Subjects N=101	Non-Rollover Subjects N=90	Total N=191	Rollover Subjects N= 109	Non-Rollover Subjects N= 103	Total N=212
Total subject-time (months) for all subjects								
Baseline period[a,b]								
8.9	42.3	51.2	91.0	293.1	384.1	99.8	335.5	435.3
DX-2930-04 study treatment period[a,c]								
239.1	429.2	668.3	2696.8	2576.2	5273.0	2935.9	3005.4	5941.3
Mean HAE attack rate in attacks/month (SD)								
Baseline period[a,b]								
1.65 (1.158)	1.54 (0.971)	1.58 (1.019)	3.67 (2.502)	2.69 (2.898)	3.21 (2.732)	3.52 (2.483)	2.55 (2.754)	3.05 (2.657)
DX-2930-04 study treatment period[a,c]								
0.20 (0.292)	0.06 (0.083)	0.11 (0.198)	0.27 (0.599)	0.25 (0.553)	0.26 (0.576)	0.27 (0.581)	0.22 (0.521)	0.25 (0.551)
Mean change HAE attack rate in attacks/month (SD)								
Treatment period change from baseline[d]								
-1.44 (0.891)	-1.48 (0.935)	-1.47 (0.896)	-3.40 (2.436)	-2.45 (2.802)	-2.95 (2.654)	-3.26 (2.410)	-2.33 (2.657)	-2.80 (2.571)
Percent change from baseline[e]								
-90.94 (9.639)	-97.08 (4.245)	-94.74 (7.257)	-92.50 (13.071)	-79.65 (103.771)	-86.53 (71.431)	-92.379 (12.8144)	-81.960 (96.7612)	-87.374 (67.7199)

C1-INH=C1-inhibitor; HAE=hereditary angioedema; LTP=long-term prophylaxis; NA=not applicable; q2wks=every 2 weeks; q4wks=every 4 weeks; SD=standard deviation

The regular dosing stage for rollover subjects began at the second dose of the study drug.

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

[b] Baseline attack rate for the rollover safety population was defined as the number of investigator-confirmed HAE attacks occurring during the run-in period of Study DX-2930-03 divided by the total number of days in the run-in period multiplied by 28 days. Baseline for the nonrollover safety population was defined as historical rate of HAE attacks in the last 3 months prior to screening divided by the number of days the subject contributed to the historical reporting period multiplied by 28 days.

[c] The DX-2930-04 treatment period investigator-confirmed HAE attack rate was calculated for each subject as the number of investigator-confirmed HAE attacks occurring during the regular dosing stage of the DX-2930-04 treatment period divided by the number of days the subject contributed to the regular dosing stage of the treatment period multiplied by 28 days.

[d] The treatment period change from baseline was calculated as the regular dosing stage HAE attack rate minus the baseline HAE attack rate.

[e] Percentage change from baseline corresponds to 100% * ((treatment period HAE attack rate in 04 study – baseline HAE attack rate)/baseline HAE attack rate).

Assessment of the Applicant's Response

The MAH has provided demographic background, medical history and efficacy outcome separately for the 21 paediatric subjects in the paediatric population.

HAE subjects who are 12 years of age or older at the time of screening were eligible for the study. The mean age in the paediatric population was 14.3 year, ranging from 12 to 18 years of age. Compared to the adult population, there were a higher proportion of male subjects (52% in the paediatric vs 30% in the adult population. The demographic characteristics were otherwise similar between the two

populations. In the adult population 75% of the subjects did not complete the study compared to 62% (13/20) in the paediatric population. 12/13 paediatric subjects not completing the study transitioned to the commercial product and one was lost to follow-up, indicating a high adherence to treatment in this population.

There was a clear difference in disease activity between the paediatric and the adult populations. In the paediatric population, 38% had experienced laryngeal attacks vs 64% in the adult population. The mean (min, max) Historical number of attacks in the last 3 months was 4.9 (1, 20) and 9.9 (0, 90) for the paediatric and adult populations , respectively, and the Baseline HAE attack rate (attacks/4 weeks) (mean [min, max]) was 1.6 (0, 4) vs 3.2 (0, 15).

The mean (SD) change HAE attack rate in attacks/month (primary endpoint) was -1.47 (0.896) in the total paediatric population. This corresponds to a percentage change from baseline of -95% in the paediatric population vs -87% in the total adult population.

In summary, there is no indication of a different efficacy outcome in the paediatric population (N=21) in Study DX-2930-04 compared to what is previously documented for Takhzyro.

Conclusion

Issue **resolved**.

Question 2

No separate information on TEAE in the paediatric population is given. The MAH is asked to provide a table similar to the table "Summary of Treatment-emergent Adverse Events Excluding HAE Attack Reported Events During the Treatment Period") for subjects <18 years, ≥18 years and the total population separately.

Summary of the MAH's response

A summary of TEAEs, excluding HAE attacks, is presented below for the paediatric, adult, and total population separately

Table 6: Summary of Treatment-emergent Adverse Events (Excluding HAE Attack Reported Events) During the Treatment Period (Safety Population)

Category	Subjects < 18 years[c] N = 21 n (%)	m	Subjects ≥ 18 years[c] N = 191 n (%)	m	Total Population[d] N = 212 n (%)	m
Total subject-time (years)[a]	52.01		428.63		480.64	
Mean subject-time (years)	2.48		2.24		2.27	
Total number of doses[b]	1328		10571		11899	
Mean number of doses	63.2		55.3		56.1	
Any TEAE	20 (95.2)	361	186 (97.4)	4029	206 (97.2)	4390
Any related TEAE	12 (57.1)	251	104 (54.5)	1869	116 (54.7)	2120
Any serious TEAE	1 (4.8)	2	20 (10.5)	29	21 (9.9)	31
Any related serious TEAE	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Any severe TEAE	2 (9.5)	3	36 (18.8)	66	38 (17.9)	69
Any related severe TEAE	0 (0.0)	0	3 (1.6)	5	3 (1.4)	5
Any investigator-reported AESI	0 (0.0)	0	13 (6.8)	26	13 (6.1)	26
Death due to TEAE	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-
Hospitalization due to TEAE	1 (4.8)	2	20 (10.5)	29	21 (9.9)	31
Discontinuation due to TEAE	0 (0.0)	-	6 (3.1)	-	6 (2.8)	-

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

[a] A year was defined as 365.25 days. Total subject-time (years) was the combined duration of subject exposure in years.

[b] Sum of all doses for all subjects.

[c] Source: [redacted]

[d] Source: [redacted]

Note: Percentages are based on all subjects in the safety population. Subjects were counted once per category per analysis population. Treatment-emergent AEs were defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment. Related TEAEs were TEAEs classified as related to study drug by the investigator. Severe TEAEs were TEAEs classified as severe (Grade 3) or life-threatening (Grade 4) by the investigator. AESIs were AEs of special interest as determined by the investigator. AESIs were defined in the protocol as hypersensitivity, hypercoagulation, and bleeding. Non-HAE attack reported AEs included the subset of AEs identified in the electronic data capture as not a reported HAE attack.

Assessment of the Applicant's Response

The MAH has provided a summary of TEAEs, excluding HAE attacks, for the paediatric, adult, and total population separately.

The total subject treatment time was markedly lower in the paediatric population (52 vs 429 patient-years), which make numerical comparisons of adverse events in the two populations difficult.

There were no meaningful differences in the proportion of subjects with any TEAE. One subject in the paediatric population, a female, was reported with serious AEs (suicide ideation and major depression). These events were not considered related to treatment by the MAH.

In summary, there is no indication of a different safety profile in the paediatric population (N=21) in Study DX-2930-04 compared to what is previously documented for Takhzyro.

Conclusion

Issue **resolved**

Question 3

The MAH is asked to provide a comprehensive summary, preferably as a table, of bleeding parameters at the time for the event, including aPTT, in all subjects reporting a bleeding event.

Summary of the MAH's response

For this analysis, the bleeding TEAE events were identified using SMQ-defined criteria as defined in the DX-2930-04 SAP. The bleeding parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), and prothrombin international ratio (INR) were assessed within 14 days prior to the bleeding event and 14 days after a bleeding event was identified. The baseline, actual, and change from baseline values for these measurements were summarized using descriptive statistics.

Since each individual subject might have multiple bleeding events, and each bleeding event might have multiple bleeding parameter measurements within a ±14-day window, the following data handling approach was used:

Baseline Summary: The baseline summary for all bleeding parameters is a subject level summary. Only subjects who had a measurement of a particular bleeding parameter(s) within the ±14-day window of the bleeding event are included. The baseline parameter is defined as the last non-missing value prior to the first exposure to the study drug (for rollover subjects, this is the baseline in the DX-2930-03 study, and for DX-2930-04 study subjects, this is the value before the first dose in the DX-2930-04 study).

Actual Value and Change from Baseline Summary: The actual value and change from baseline summaries are an event-level summary. All bleeding parameter measurements within ±14 days of a bleeding event are included. If there were multiple measurements for a particular bleeding parameter, the measurement closest to the date of the bleeding event was used in the analysis. If the bleeding parameter measurement was taken on the same day as the bleeding event, and the time of the bleeding event or bleeding parameter measurement was missing, then the bleeding parameter measurement was considered to be taken after the bleeding event.

Table 7 provides a summary of the bleeding parameters ±14 days of an SMQ-defined bleeding event in Study DX-2930-04. The same parameters from the total population in the study are included in the table as reference.

To further differentiate systemic and local bleeding events, subsets of bleeding events that were either injection site related bleeding events or non-injection site related bleeding events were identified. A summary of these results can be found in Module 5.3.5.2 (not included for the sake of conciseness).

A total of 52 subjects with 161 SMQ-defined bleeding events with a clear event date were identified in the analysis. As shown in Table 7, baseline mean values of aPTT, PT and INR were similar between subjects with the bleeding events and the total study population. Actual and mean changes in these parameters, before and after the bleeding events during the treatment period, were also comparable to the reference values from the total subjects in this study. In addition, similar observations were found in separate analyses based on injection site SMQ-defined bleeding events and non-injection site bleeding events (not included for the sake of conciseness).

Table 7: Summary of bleeding parameters (aPTT, PT, and INR) within 14 days before and after an SMQ-defined bleeding event and from total population (Safety Population)

	Summary of Bleeding Parameters		
	14 Days Prior to Bleeding TEAE[a]	**14 Days After a Bleeding TEAE[a]**	**Total Population[b]**
aPTT (sec)			
Baseline			
n[c]	10	30	212
Mean (SD)	30.62 (4.888)	28.53 (4.706)	28.40 (4.210)
Median	30.45	27.55	27.90
Min, Max	23.3, 39.3	23.3, 42.3	18.3, 49.1
Treatment Period – Actual Values			
m[d]	14	55	-[e]
Mean (SD)	36.34 (6.325)	33.77 (6.116)	33.18 (6.557)
Median	34.05	33.40	31.85
Min, Max	28.2, 50.8	24.3, 62.7	24.5, 69.9
Treatment Period - Δ Baseline[f]			
m[d]	14	55	-[e]
Mean (SD)	5.77 (5.944)	4.42 (7.539)	5.01 (5.913)
Median	4.85	4.00	4.70
Min, Max	-3.8, 19.3	-8.0, 38.2	-11.6, 44.4
INR			
Baseline			
n[c]	10	30	212
Mean (SD)	1.10 (0.151)	1.05 (0.137)	1.075 (0.1629)
Median	1.07	1.01	1.045
Min, Max	1.0, 1.4	0.9, 1.5	0.83, 2.36
Treatment Period – Actual Values			
m[d]	14	55	-[e]
Mean (SD)	1.05 (0.060)	1.05 (0.081)	1.080 (0.1601)
Median	1.06	1.04	1.050
Min, Max	1.0, 1.2	0.9, 1.3	0.86, 2.54
Treatment Period - Δ Baseline[f]			
m[d]	14	55	-[e]
Mean (SD)	-0.02 (0.151)	0.02 (0.105)	0.000 (0.1532)
Median	0.03	0.03	0.010
Min, Max	-0.3, 0.2	-0.3, 0.4	-0.78, 0.53

PT (sec)			
Baseline			
n[c]	10	30	212
Mean (SD)	12.12 (1.612)	11.62 (1.507)	11.88 (1.850)
Median	11.70	11.20	11.40
Min, Max	10.5, 15.8	9.7, 16.3	9.1, 27.6
Treatment Period – Actual Values			
m[d]	14	55	-[e]
Mean (SD)	11.69 (0.576)	11.76 (0.920)	11.90 (1.811)
Median	11.60	11.60	11.60
Min, Max	10.7, 12.6	9.9, 14.7	9.4, 28.5
Treatment Period - Δ Baseline[f]			
m[d]	14	55	-[e]
Mean (SD)	-0.14 (1.543)	0.31 (1.130)	-0.01 (1.658)
Median	0.30	0.30	0.10
Min, Max	-3.2, 2.1	-3.7, 4.5	-8.6, 5.6

aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time

AEs of bleeding were defined using a standard MedDRA query (SMQ) and with non-missing date are included in this analysis.

[a] Source: [redacted]

[b] Source: [redacted]

[c] n = number of subjects experiencing the event. For the total population, n = total number of subjects in safety population of study DX-2930-04.

[d] m = number of bleeding events with bleeding parameter value within the specified time period.

[e] For the change from baseline values for the total population, the number of subjects for each bleeding parameter were the following: n=156 for aPTT; n=157 for INR and PT.

[f] Change from baseline values for the total population are presented from Day 910 / Week 130 which corresponds to the last visit lanadelumab was administered and laboratory assessments were performed in study DX-2930-04.

Assessment of the Applicant's Response

aPTT, PT and INR before and after the bleeding events during the treatment period, were comparable in 52 subjects with 161 SMQ-defined bleeding events to the reference values from the total subjects in this study. There is thus no indication that the bleeding events were related to any alterations in these bleeding parameters.

Conclusion

Issue **resolved**.

2.3.4. Discussion on clinical aspects

During the assessment of Study DX-2930-04 in procedure EMEA/H/C/004806/P46/001, there were three remaining issues in need of further clarification before the requirements stipulated in Article 46

of the Paediatric Legislation and the additional pharmacovigilance activity category 3 PASS could be considered fulfilled. These issues are addressed in the current procedure.

The MAH has provided demographic background, medical history and efficacy outcome separately for the 21 paediatric subjects in the paediatric population.

HAE subjects who are 12 years of age or older at the time of screening were eligible for the study. The mean age in the paediatric population was 14.3 year, ranging from 12 to 18 years of age. Compared to the adult population, there were a higher proportion of male subjects (52% in the paediatric vs 30% in the adult population). The demographic characteristics were otherwise similar between the two populations. In the adult population, 75% of the subjects did not complete the study compared to 62% (13/20) in the paediatric population. 12/13 paediatric subjects not completing the study transitioned to the commercial product and one was lost to follow-up, indicating a high adherence to treatment in this population.

There was a clear difference in disease activity between the paediatric and the adult populations with Baseline HAE attack rate (attacks/4 weeks) (mean [min, max]) 1.6 (0, 4) vs 3.2 (0, 15) for the paediatric and adult populations, respectively. The mean (SD) change HAE attack rate in attacks/month (primary endpoint) was -1.47 (0.896) in the total paediatric population. This corresponds to a percentage change from baseline of -95% in the paediatric population vs -87% in the total adult population.

The MAH also provided a summary of TEAEs, excluding HAE attacks, for the paediatric, adult, and total population separately.

The total subject treatment time was markedly lower in the paediatric population (52 vs 429 patient-years), which make numerical comparisons of adverse events in the two populations difficult. However, there were no meaningful differences in the proportion of subjects with any TEAE. One subject in the paediatric population, a female, was reported with serious AEs (suicide ideation and major depression). These events were not considered related to treatment by the MAH.

In summary, there is no indication of a different outcome of efficacy parameters or a different safety profile in the paediatric population in Study DX-2930-04 compared to what is previously documented for Takhzyro.

The MAH provided data on aPTT, PT and INR before and after the bleeding events during the treatment period, showing comparable levels in 52 subjects with SMQ-defined bleeding events to the reference values from the total subjects in this study. There is thus no indication that the bleeding events were related to any alterations in these bleeding parameters.

Takhzyro is currently indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older. It is agreed with the MAH that no update of the PIL or other actions are warranted. The B/R for Takhzyro in the approved indication is considered unchanged.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

☐ **Not fulfilled:**

4. Additional clarification requested

None