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Lanadelumab (hereditary angioedema) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Lanadelumab (hereditäres Angioödem) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 August 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAE	hereditary angioedema
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug lanadelumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 12 May 2021.

Research question

The aim of the present report is the assessment of the added benefit of lanadelumab in comparison with the appropriate comparator therapy (ACT) in patients aged 12 years and older for routine prevention of recurrent attacks of hereditary angioedema (HAE).

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of lanadelumab

Therapeutic indication	ACT[a]
Patients aged 12 years and older for routine prevention of recurrent attacks of HAE[b, c]	Routine prevention with C1 esterase inhibitor
a. Presentation of the ACT specified by the G-BA. b. The therapeutic indication of lanadelumab is assumed to comprise only patients with type I or type II HAE. c. Both study arms should offer the possibility of acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema	

The company named routine prophylaxis with C1 esterase inhibitor as ACT, and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

The check of the completeness of the study pool identified no relevant study for the comparison of lanadelumab with the ACT specified by the G-BA.

The company presented the non-randomized PATCH study and 2 non-randomized before-after comparisons for the assessment of the added benefit of lanadelumab.

None of the studies or analyses presented by the company is suitable for the derivation of an added benefit of lanadelumab in comparison with the ACT in patients aged 12 years and older for routine prevention of recurrent attacks of HAE.

Study PATCH

The PATCH study is a retrospective comparison of individual patient data from the studies HELP, HELP-OLE and CHANGE-3 on lanadelumab or C1 esterase inhibitor (for intravenous use) with adjustment for confounders. In the planning and conduct of the study, the company took into account individual aspects of the methods described in rapid report A19-43 for the generation of routine practice data and their analysis for the purpose of the benefit assessment. Overall, however, the PATCH study is not suitable for the derivation of an added benefit of lanadelumab in comparison with the ACT specified by the G-BA. The main reasons for this are the following:

- The included patient populations show a marked structural inequality with regard to the confounders recorded, which cannot be sufficiently compensated for by means of confounder adjustment.
- The information available in the data set on the confounders identified as relevant by the company is incomplete, and the company did not draw any conclusions from this.
- Not all relevant studies on the comparator side were included in the analysis, and the company did not address the effects of this on the results of the PATCH study.

Overall, the analyses presented by the company in the context of the PATCH study do not allow an adequate comparison of lanadelumab with the ACT.

Before-after comparisons

The before-after comparisons presented by the company on the basis of post-hoc analyses of the randomized controlled trial (RCT) HELP and a prospective observational study do not allow a balancing for the added benefit. The following reasons are relevant for this:

- The treatment situations in the post-hoc analysis of the RCT HELP are not sufficiently comparable between “before” and “after”. The treatment with C1 esterase inhibitor took place under uncontrolled conditions outside the study, whereas the treatment with lanadelumab took place under controlled study conditions. This discrepancy in study conditions between before and after can potentially lead to a major bias in the results.
- Neither of the 2 before-after comparisons presented by the company reported outcomes of the category of side effects. A balancing for the added benefit is therefore not possible.

Summary

Thus, the company presented no suitable data for the assessment of the added benefit of lanadelumab in its dossier. This resulted in no hint of an added benefit of lanadelumab in comparison with the ACT in patients aged 12 years and older for routine prevention of recurrent attacks of HAE. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of lanadelumab.

Table 3: Lanadelumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients aged 12 years and older for routine prevention of recurrent attacks of HAE[b, c]	Routine prevention with C1 esterase inhibitor	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. The therapeutic indication of lanadelumab is assumed to comprise only patients with type I or type II HAE. c. Both study arms should offer the possibility of acute treatment of HAE attacks. ACT: appropriate comparator therapy ; G-BA: Federal Joint Committee; HAE: hereditary angioedema		

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2019, where the G-BA had determined a considerable added benefit of lanadelumab on the basis of the RCT HELP. However, in that assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs; a comparison with the ACT was not required.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report is the assessment of the added benefit of lanadelumab in comparison with the ACT in patients aged 12 years and older for routine prevention of recurrent attacks of HAE.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of lanadelumab

Therapeutic indication	**ACT[a]**
Patients aged 12 years and older for routine prevention of recurrent attacks of HAE[b, c]	Routine prevention with C1 esterase inhibitor
a. Presentation of the ACT specified by the G-BA. b. The therapeutic indication of lanadelumab is assumed to comprise only patients with type I or type II HAE. c. Both study arms should offer the possibility of acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema	

The company named routine prophylaxis with C1 esterase inhibitor as ACT, and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on lanadelumab (status: 22 February 2021)
- bibliographical literature search on lanadelumab (last search on 22 February 2021)
- search in trial registries/trial results databases for studies on lanadelumab (last search on 22 February 2021)
- search on the G-BA website for lanadelumab (last search on 22 February 2021)
- bibliographical literature search on the ACT (last search on 22 February 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 22 February 2021)
- search on the G-BA website for the ACT (last search on 22 February 2021)

To check the completeness of the study pool:

- search in trial registries for studies on lanadelumab (last search on 20 May 2021); for search strategies, see Appendix A of the full dossier assessment

The check of the completeness of the study pool identified no relevant study for the comparison of lanadelumab with the ACT specified by the G-BA.

In Module 4 A, the company presented the RCT HELP for a direct comparison of lanadelumab against placebo. However, as this study did not allow a comparison with the ACT and the company also did not identify any suitable studies for an adjusted indirect comparison with a common comparator, it presented the non-randomized PATCH study and 2 non-randomized before-after comparisons. The company mainly used the PATCH study for the benefit assessment.

None of the studies or analyses presented by the company is suitable for the derivation of an added benefit of lanadelumab in comparison with the ACT in patients aged 12 years and older for routine prevention of recurrent attacks of HAE. This is explained in the following sections.

2.3.1 Direct comparison

RCT HELP

The HELP study [3-8] is a double-blind RCT on the comparison of lanadelumab with placebo for routine prevention of recurrent attacks of HAE. It included patients ≥ 12 years of age with documented diagnosis of type I or II HAE.

Hence, this study did not compare lanadelumab against the ACT, but against placebo. The HELP study is therefore not suitable for the research question of the present benefit assessment. This concurs with the assessment of the company, which also described that the HELP study did not allow a comparison with the ACT.

2.3.2 Non-randomized comparisons

2.3.2.1 Study PATCH

The PATCH study [9] is a retrospective comparison of individual patient data from 3 studies on lanadelumab or C1 esterase inhibitor (for intravenous use) with adjustment for confounders. In the planning and conduct of the study, the company took into account individual aspects of the methods described in rapid report A19-43 for the generation of routine practice data and their analysis for the purpose of the benefit assessment [10]. Overall, however, the PATCH study is not suitable for the derivation of an added benefit of lanadelumab in comparison with the ACT specified by the G-BA. The main reasons for this are the following:

- The included patient populations show a marked structural inequality with regard to the confounders recorded, which cannot be sufficiently compensated for by means of confounder adjustment.

- The information available in the data set on the confounders identified as relevant by the company is incomplete, and the company did not draw any conclusions from this.
- Not all relevant studies on the comparator side were included in the analysis, and the company did not address the effects of this on the results of the PATCH study.

The non-randomized comparison presented by the company within the framework of the PATCH study is described below and detailed reasons are given as to why the analyses do not allow an assessment of the added benefit of lanadelumab in comparison with the ACT. Further information on the study characteristics is presented in Appendix B of the full dossier assessment.

Information retrieval

The company stated that it had conducted a systematic evidence search for relevant studies and possible confounders for the PATCH study, which it had supplemented with the information retrieval for non-randomized comparative studies and further investigations presented in Module 4 A. This information retrieval of the company for the PATCH study is not presented in its entirety in Module 4 A. The company referred to an information retrieval in the statistical analysis plan (SAP) for the PATCH study, which is not fully documented there, however. The information retrieval for the PATCH study, including the search for relevant confounders, is therefore overall not comprehensible.

Data sources

In the PATCH study, the company included data from the RCT HELP and the associated single-arm extension study HELP-OLE for lanadelumab and data from the single-arm extension study CHANGE-3 for the comparator therapy. The company did not use another study identified as relevant in the information retrieval (COMPACT-OLE [11]) because the company did not have access to the individual patient data.

The approach of the company was not appropriate. In principle, it is understandable that the company did not include the COMPACT-OLE study in the analysis if it had no access to the individual patient data. However, it is necessary that adequate consequences are drawn from the non-consideration of these relevant data. It would at least be necessary to assess what effects the exclusion of the COMPACT-OLE study has on the results of the PATCH study. Such an assessment was not presented by the company, however. This is particularly problematic because the COMPACT-OLE study investigated a possibly more effective subcutaneous formulation of C1 esterase inhibitor [12].

The studies used by the company as data sources and their subpopulations used for the PATCH study are described below.

RCT HELP (lanadelumab)

As already described in Section 2.3.1, the HELP study is a double-blind RCT on the comparison of lanadelumab with placebo for routine prevention of recurrent attacks of HAE. It included patients ≥ 12 years of age with documented diagnosis of type I or II HAE. Patients ≥ 18 years of age who were receiving routine drug prophylaxis of HAE attacks before the start of the study had to discontinue this medication in a 2-week wash-out period. A total of 126 patients were included and allocated to the treatment arms in a 2:1 randomization (150 mg lanadelumab subcutaneously every 4 weeks [n = 28], 300 mg lanadelumab every 4 weeks [n = 29], 300 mg lanadelumab every 2 weeks [n = 27], placebo [n = 41]; according to the company, 1 patient received no study medication). The primary outcome of the study was the number of investigator-confirmed HAE attacks per patient. Further outcomes of the categories of morbidity and side effects were recorded. The patients received the study medication for 26 weeks. The patients then either received follow-up observation for 8 weeks or were directly included in the extension study HELP-OLE (see below).

For the PATCH study, the company used the 27 patients from the lanadelumab arm who were treated with the approval-compliant starting dose of 300 mg every 2 weeks.

Extension study HELP-OLE (lanadelumab)

The HELP-OLE study [13-15] is an open-label single-arm extension study of the RCT HELP described above. It included both patients from the RCT HELP (= rollover) and new patients ≥ 12 years with type I or II HAE (non-rollover). The rollover patients had to have completed the RCT HELP to qualify for participation in HELP-OLE. The non-rollover patients had to meet similar eligibility criteria as for inclusion in the RCT HELP in order to participate in the HELP-OLE study, but patients only had to have 1 HAE attack within 12 weeks (instead of 4 weeks in the HELP study) to qualify for study participation. A total of 212 patients were included in the study (rollover n = 109; non-rollover n = 103). The rollover patients received a single dose of 300 mg lanadelumab subcutaneously and were observed until the development of an HAE attack. Only then did these patients receive an approval-compliant dosing of lanadelumab 300 mg subcutaneously every 2 weeks until the end of the study. The non-rollover patients, in contrast, received lanadelumab 300 mg every 2 weeks directly after study inclusion until the end of the study. The primary outcome of the study was long-term safety. Further relevant outcomes were recorded in the category of morbidity. The maximum treatment duration was 924 days (132 weeks), which was followed by an observation period of 4 weeks.

For the PATCH study, the company used 84 of the 103 non-rollover patients (19 patients were excluded because they had received an unapproved dosage of lanadelumab in a previous study). The rollover patients were not included in the PATCH study due to the different number of lanadelumab doses for each individual patient.

Extension study CHANGE-3 (C1 esterase inhibitor)

The CHANGE-3 study [16,17] is an open-label single-arm extension study of the randomized placebo-controlled crossover study CHANGE-1 Part B [18,19]. The study included patients aged ≥ 1 year with type I or II HAE who had a history of ≥ 1 HAE attack per month or of any laryngeal attacks. A total of 146 patients were enrolled in the study. 16 patients had previously participated in the study CHANGE-1 Part B (= rollover). The patients received 1000 international units of C1 esterase inhibitor intravenously every 3 to 7 days. Primary outcome of the study was the frequency of HAE attacks. Further relevant outcomes were recorded in the categories of morbidity and side effects. The average treatment of the patients was 243.5 days (about 35 weeks), maximum treatment was 2.6 years (about 136 weeks). This was followed by an observation period of 12 weeks.

For the PATCH study, the company used 120 of the 146 patients from the CHANGE-3 study (26 patients were excluded by the company because they did not concur with the inclusion criteria of the HELP study or with the approved therapeutic indication of lanadelumab).

Confounder identification, recording and adjustment in the PATCH study

Since the necessary structural equality between the treatment groups is not guaranteed in non-randomized studies, group differences in possible confounders, i.e. factors that are related to both the treatment and outcomes and can thus alter a treatment effect, must be taken into account in the effect estimation. The first prerequisite for this is that relevant confounders are systematically identified. Then it must be ensured that the data set used contains the necessary information on the identified confounders. Based on this, a sufficient overlap (similar probability of allocation to one of the 2 treatment options) and structural equality between the treatment groups must be established using suitable adjustment methods (e.g. propensity score weighting). In the following, the procedure of the company as well as the deficiencies in the confounder identification, recording and adjustment, which led to the exclusion of the PATCH study, are described.

Identification of confounders in the PATCH study

The company stated that it had conducted a systematic literature search to identify relevant confounders (see above). In the next step, the company had presented the identified confounders to 2 clinical experts for validation. A total of 5 categories with potential confounders and their respective characteristics for consideration in clinical studies were confirmed by the clinical experts (e.g. age, sex, clinical history).

The company’s approach for identifying confounders was based on the specifications of rapid report A19-43, but, as described above, the approach for the information retrieval was not sufficiently documented and is therefore not comprehensible.

Confounders not completely recorded in the data sources used

The data sources used by the company only contain information on some of the confounders it had identified as relevant. In particular, there is a lack of information on general health status (body weight/body mass index, health-related quality of life), clinical history (baseline C1 esterase inhibitor activity) and previous routine prophylaxis (response to previous routine prophylaxis, type and extent of previous routine prophylaxis).

The company did not draw any conclusions from the missing data on these confounders identified as relevant. This is not appropriate, as the possible influence that the missing information on relevant confounders has on the certainty of results and on the observed effects of the PATCH study was thus not addressed. For example, there is no assessment of how a missing adjustment for potentially relevant confounders could affect the effect estimation of individual outcomes and of the extent of an observed effect at which a sufficiently reliable conclusion, for example on an added benefit, is still possible.

Structural equality of the patient populations was not achieved by adjustment

Despite the lack of information on relevant confounders in the data set used, the company at least attempted to establish structural equality between the patient populations with the available confounders by means of adjustment. For this purpose, it used a propensity score weighting by means of fine stratification weights according to Desai and Franklin [20].

This showed that previous routine prophylaxis of HAE greatly increased the probability of receiving treatment with lanadelumab. Since in the lanadelumab arm, in contrast to the C1 esterase inhibitor arm of the PATCH study, a large proportion of patients had already been pretreated with routine prophylaxis, the overlap of the propensity scores of the 2 populations is very small and overall insufficient (see Figure 1).

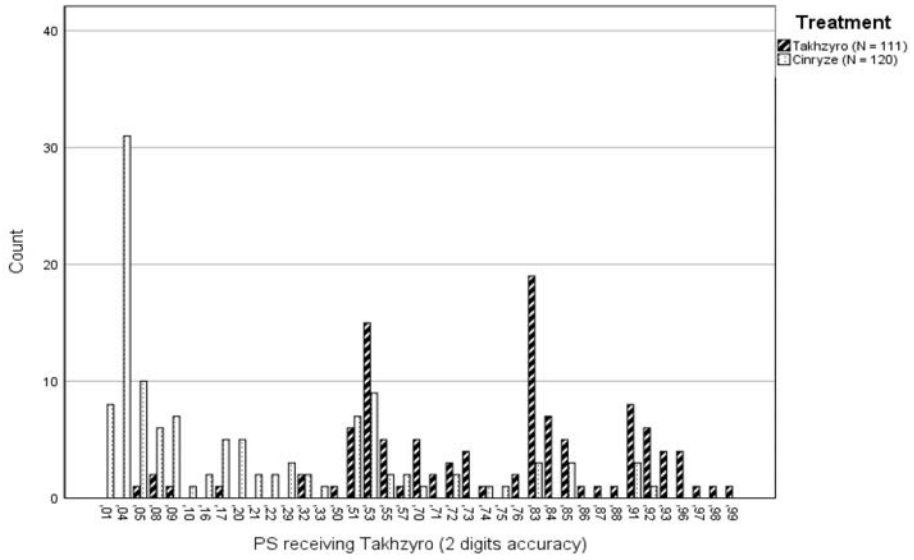

Figure 1: Distribution of the propensity score in the PATCH study (Takhzyro = lanadelumab; Cinryze = C1 esterase inhibitor)

This also shows that, overall, the confounders recorded at baseline are not sufficiently balanced and also cannot be sufficiently balanced, and that consequently there is a pronounced structural inequality between the patient populations. The structural equality also remains after using the fine stratification weights.

The company therefore correctly assessed the overlap of the propensity score distribution and the achieved balance of the fine stratification weights as insufficient and rejected the adjustment using propensity scores. Instead, it carried out an adjustment by means of regression analysis (generalized linear model). However, the small overlap of the propensity scores in Figure 1 shows that completely different patient populations were compared within the PATCH study and that the data set used by the company is therefore not suitable for a meaningful comparison of lanadelumab and C1 esterase inhibitor, regardless of the method chosen for the confounder adjustment. Accordingly, the structural inequality cannot be meaningfully compensated for by means of confounder adjustment. The alternative adjustment carried out by the company by means of a regression model after the adjustment by means of propensity scores had failed also did not eliminate the pronounced structural differences of the included patient populations.

Summary

Overall, the analyses presented by the company in the context of the PATCH study do not allow an adequate comparison of lanadelumab with the ACT.

Further deficiencies of the PATCH study

The PATCH study has further deficiencies, 2 of which are described below as supplementary information.

No adequate justification of the analysis date of the PATCH study

The company conducted the analysis of all outcomes of the PATCH study at the time point of 26 weeks. However, the data sources HELP-OLE and CHANGE-3 used for the PATCH study have treatment and observation periods of up to 2.6 years. The company did not provide sufficient justification in terms of content for the selection of the date of analysis of 26 weeks.

Statistical analysis plan was not prepared without knowledge of the data

As described in rapid report A19-43, also for routine practice data, an SAP and a study protocol should be prepared that prespecify the essential aspects of the study. In retrospective study designs, this should be done without knowledge of the data.

At the time of the preparation of the SAP for the PATCH study, all studies used by the company as a data source for the PATCH study had already been completed. Therefore, it cannot be ensured that the SAP for the PATCH study was prepared without knowledge of the data. This cannot be assumed, in particular, because descriptive presentations and calculations based on the final study population size were already made in the SAP. The company did not present a study protocol for the PATCH study.

2.3.2.2 Before-after comparisons

Prospective observational study by Hahn 2020

The study by Hahn 2020 [21] is a prospective observational study in adult patients with HAE. Patients with type I or II HAE with inadequate symptom control with on-demand treatment with icatibant or C1 esterase inhibitor, or with inadequate symptom control on routine prophylaxis with C1 esterase inhibitor were eligible for inclusion. A total of 12 patients were included and received 6-month treatment with a routine prophylaxis with lanadelumab (300 mg every 2 weeks). Outcomes of the categories of morbidity and health-related quality of life were recorded.

For the before-after comparison, the company only included patients who had already received routine prophylaxis with C1 esterase inhibitor before the start of the study. This applied to 3 patients. For these patients, the company compared the monthly number of HAE attacks and health-related quality of life after 6 months of treatment with lanadelumab with the period of the last 6 months before study inclusion.

Post-hoc analysis of the RCT HELP

The company presented a retrospective before-after comparison of patients from the RCT HELP (see Section 2.3.2.1 for a description of the RCT HELP). This analysis includes patients for whom prior routine prophylaxis with C1 esterase inhibitor was documented at enrolment and who received routine prophylaxis with 300 mg lanadelumab every 2 (n = 14) or every 4 weeks (n = 19) in the randomized treatment phase. The outcome was the monthly number of HAE attacks under lanadelumab during the randomized treatment phase in the RCT HELP

compared with the previous number of HAE attacks under C1 esterase inhibitor outside the study documented at enrolment.

Before-after comparisons unsuitable for the assessment of the added benefit

The before-after comparison presented by the company do not allow a balancing for the added benefit. The following reasons are relevant for this:

- The treatment situations in the post-hoc analysis of the RCT HELP are not sufficiently comparable between "before" and "after". The treatment with C1 esterase inhibitor took place under uncontrolled conditions outside the study, whereas the treatment with lanadelumab took place under controlled study conditions. This discrepancy in study conditions between before and after can potentially lead to a major bias in the results.
- Neither of the 2 before-after comparisons presented by the company reported outcomes of the category of side effects. A balancing for the added benefit is therefore not possible.

2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of lanadelumab in its dossier. This resulted in no hint of an added benefit of lanadelumab in comparison with the ACT in patients aged 12 years and older for routine prevention of recurrent attacks of HAE. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of lanadelumab in comparison with the ACT is summarized in Table 5.

Table 5: Lanadelumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients aged 12 years and older for routine prevention of recurrent attacks of HAE[b, c]	Routine prevention with C1 esterase inhibitor	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. The therapeutic indication of lanadelumab is assumed to comprise only patients with type I or type II HAE. c. Both study arms should offer the possibility of acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema		

The assessment described above deviates from that of the company, which claimed a hint of considerable added benefit.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the framework of the market access in 2019, where the G-BA had determined a considerable added benefit of lanadelumab on the basis of the RCT HELP. However, in that assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs; a comparison with the ACT was not required.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Banerji A, Riedl MA, Bernstein JA et al. Effect of Lanadelumab Compared with Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA 2018; 320(20): 2108-2121. https://dx.doi.org/10.1001/jama.2018.16773.

4. Dyax. 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) [online]. [Accessed: 18.05.2021]. URL: https://www.pharmnet-bund.de/dynamic/de/arzneimittel-informationssystem/index.html.

5. Dyax. 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) [online]. [Accessed: 25.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003943-20.

6. Lumry WR, Weller K, Magerl M et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. Allergy 2020. https://dx.doi.org/10.1111/all.14680.

7. Shire. Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE [online]. 2019 [Accessed: 25.05.2021]. URL: https://ClinicalTrials.gov/show/NCT02586805.

8. Riedl MA, Maurer M, Bernstein JA et al. Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks. Allergy 2020; 75(11): 2879-2887. https://dx.doi.org/10.1111/all.14416.

9. Takeda. PATient level comparison of Efficacy and Safety of Takhzyro vs. Cinryze based on CHANGE and HELP studies (PATCH) according to IQWiG methodology; study report [unpublished]. 2021.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V; Rapid Report [online]. 2020 [Accessed: 02.06.2020]. URL: https://www.iqwig.de/download/A19-43_Versorgungsnahe-Daten-zum-Zwecke-der-Nutzenbewertung_Rapid-Report_V1-1.pdf.

11. Craig T, Zuraw B, Longhurst H et al. Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks. J Allergy Clin Immunol Pract 2019; 7(6): 1793-1802.e2. https://dx.doi.org/10.1016/j.jaip.2019.01.054.

12. European Medicines Agency. Takhzyro; Orphan Maintenance Assessment Report [online]. 2018 [Accessed: 20.07.2021]. URL: https://www.ema.europa.eu/documents/orphan-maintenance-report/takhzyro-epar-orphan-maintenance-assessment-report-initial-authorisation_en.pdf.

13. Dyax. 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) [online]. [Accessed: 25.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-005255-27.

14. Riedl MA, Bernstein JA, Craig T et al. A Phase 3 open-label extension study of the efficacy and safety of lanadelumab for the prevention of angioedema attacks in patients with hereditary angioedema: Trial design. Allergy Asthma Clin Immunol 2017; 13(Supplement 2). https://dx.doi.org/10.1186/s13223-017-0198-5.

15. Shire. Long-term Safety and Efficacy Study of DX-2930 (SHP643) to Prevent Acute Angioedema Attacks in Patients With Type I and Type II HAE [online]. 2020 [Accessed: 25.05.2021]. URL: https://ClinicalTrials.gov/show/NCT02741596.

16. Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. Am J Med 2012; 125(9): 938. https://dx.doi.org/10.1016/j.amjmed.2012.02.020.

17. Shire. Open-Label C1 Esterase Inhibitor (C1INH-nf) for the Prevention of Acute Hereditary Angioedema (HAE) Attacks (CHANGE 3) [online]. 2021 [Accessed: 15.07.2021]. URL: https://ClinicalTrials.gov/show/NCT00462709.

18. Zuraw BL, Busse PJ, White M et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med 2010; 363(6): 513-522. https://dx.doi.org/10.1056/NEJMoa0805538.

19. Lumry WR, Miller DP, Newcomer S et al. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. Allergy Asthma Proc 2014; 35(5): 371-376. https://dx.doi.org/10.2500/aap.2014.35.3783.

20. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ 2019; 367: l5657. https://dx.doi.org/10.1136/bmj.l5657.

21. Hahn J, Trainotti S, Wigand MC et al. Prospective Analysis in Patients With HAE Under Prophylaxis With Lanadelumab: A Real-life Experience. J Drugs Dermatol 2020; 19(10): 978-983. https://dx.doi.org/10.36849/JDD.2020.5269.

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