Nye metoder - Request for assessment of medicinal product

To request an assessment of a new medicinal product or a new indication for an existing medicinal product through Nye metoder, health technology developers should complete this form. By submitting a request for assessment, the developer signals that it plans to submit documentation for such an assessment.

Please send the completed form to Nye metoder by e-mail: nyemetoder@helse-sorost.no.

A request for assessment may not be submitted prior to day 120 of the European Medicines Agency (EMA) marketing authorisation assessment process for new medicinal products under regular approval procedure, or prior to day 1 for variation/extension assessments and for medicinal products under accelerated assessment.

This form must be completed in its entirety. Nye metoder will plan the assessment process based on the information provided in the request form.

At the time of request for assessment, the health technology developer must have a plan for when it intends to submit documentation for assessment.

Information about Nye metoder can be found online (nyemetoder.no). Please contact Sekretariatet for Nye metoder if you have any questions.

Please note: The form will be published in its entirety.

The submitter is aware that the form will be published in its entirety (**tick**): ☑

1 Contact information	
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External representation Name/Organization Phone/E-mail *PLEASE NOTE: For external representation, please attach an authorisation/power of attorney*	N/A

2 Medicinal product overview

Does the request concern a new active substance?	Yes
Trade name	To be confirmed
Generic name	Garadacimab
Marketing authorisation in Norway	Currently under assessent by EMA
ATC code	To be confirmed
Mode of administration	Administered subcutaneously, once monthly.
Pharmacotherapeutic group and mechanism of action *Briefly describe*	Garadacimab is a first-in-class recombinant monoclonal antibody inhibiting Factor XIIa (anti-FXIIa mAb). Garadacimab is a fully human IgG4/lambda recombinant monoclonal antibody which binds to the catalytic domain of activated Factor XII (FXIIa and βFXIIa) and inhibits its catalytic activity. The inhibition of FXIIa, the first factor activated in the contact system, prevents HAE attacks by blocking the activation of prekallikrein to kallikrein and the generation of bradykinin, which is associated with inflammation and swelling in HAE attacks.
Expected indication relevant to the request *Expected indication must be written in Norwegian*	For rutinemessig forebygging av residiverende anfall av hereditært angioødem (HAE) hos pasienter ≥12 år.

3 Assessment history

Has the medicinal product previously been assessed by Nye metoder for other indications? *If yes, enter the Nye metoder ID number*	No
Are you aware of other medicinal products assessed by Nye metoder for the same indication? *If yes, enter the Nye metoder ID number*	Takhzyro (ID2022_100), Orladeyo (ID2021_048), Berinert for subcutaneous use (ID2019_020)

4 Expected timeline	
Procedure number for the marketing authorisation assessment in EMA	Not public info
Expected date (month/year) of CHMP positive opinion	Late 2024
Expected date (month/year) of marketing authorisation in Norway	Early 2025
Expected date (quarter/year) for submission of documentation to Norwegian Medicines Agency *Dates must be stated*	Early 2025

5 Diagnostics and resource use Fill inn where relevant	
Will the new method require diagnostic testing for biomarker analysis?	No
Which biomarker(s) are relevant and which publications describe this? *Please refer to publications*	N/A
Do you know whether diagnostics can be performed by the public health service or whether it must be performed by an external supplier?	N/A
Will introduction of the new method require establishment of other/new infrastructure? *For example, custom analysis machine, digital pathology/ AI-based analysis, proteomics, functional tests etc.?*	No
Pre-analytical requirements *For example, biopsies, other sampling, sample processing etc. are required.*	N/A

Test execution: is there a need to establish one specific test or is a biomarker already established in the health service (e.g. in gene panels)?	No
Description of reading of results including data analysis program if necessary.	N/A
Which patient groups need to be tested, and what is the expected proportion of findings that provide treatment options?	N/A

6 Description of the disease and current treatments

Description of the disease *<u>Brief</u> description of the pathophysiology and clinical presentation/symptoms, possibly including references*	The normal biological role of C1-INH in the immune response is to regulate activation of blood-based systems involved in inflammation and coagulation (Zuraw and Christiansen 2011). The bradykinin-forming cascade, also called the plasma contact system, plays a crucial role in vasodilation, blood coagulation, and fibrinolysis (Busse and Kaplan 2022). In patients with HAE, the C1-INH protein is deficient or defective, which ultimately leads to the uncontrolled activation of the contact system and continuous production of kallikrein, which can lead to vascular leakage and oedema in the submucosal space (i.e., an HAE attack) (Lopez Lera 2021, Sinnathamby et al. 2023). Many of the symptoms experienced by patients with HAE, including oedema, pain, and dry cough, are mediated through the unregulated release of bradykinin (Sinnathamby et al. 2023). HAE is characterized by recurrent swelling of the skin (e.g., extremities, face, and genitals) and gastrointestinal attacks (e.g., painful abdominal cramps) and/or laryngeal oedema. Episodes of HAE are unpredictable, painful, and, if not treated, potentially life-threatening, which causes stress for both patients and caregivers (Maurer et al. 2022).
Therapeutic area *Specify which field best describes the method*	Hjerte- og karsykdommer Hudsykdommer **Immunologi** Infeksjonssykdommer Kreftsykdommer (velg kreftområde i neste kolonne)*
Cancer *If the method applies to the medical field of cancer, specify which type of cancer is relevant*	*** Ingen Kreftsykdom** Bein- og bløtvevskreft Blod- beinmargs- og lymfekreft Brystkreft Mage- og tarmkreft
Current treatment *Current standard treatment in Norway, including references*	There are no national guidelines or other relevant Norwegian treatment guidelines for HAE. Norwegian treatment guidelines refer to The International WAO/EAACI guidelines HAE 2021 (Norsk Helseinformatikk 2019). Current standard treatment in Norway: Plasma-derived C1 inhibitors indicated for preventive treatment (Cinryze given intravenously). Subcutaneous Berinert is indicated for preventive treatment but has not received Beslutningsforum decision to be introduced in clinical practice (ID2019_020). In clinical practice, intravenous Berinert is also used as preventive treatment. In the RHF recommendation applicable from February 1, 2024, Orladeyo (berotralstat) is 1st choice, intravenous Cinryze 2nd choice and intravenous Berinert 3rd choice for preventive treatment. Orladeyo (berotralstat) received decision from Beslutningsforum to be introduced in clinical practice in 2021 with conditions (New Methods ID2021_048). Takhzyro (lanadelumab) received decision from Beslutningsforum to be introduced in clinical practice in 2024 with conditions (New Methods ID2022_100). (The Norwegian Medicines Agency 2024)

Prognosis *Describe the prognosis with current treatment options, including references*	As HAE is a chronic condition, with a lifelong risk of sudden-onset, unpredictable, disabling, and potentially life-threatening recurrent HAE attacks, which causes stress for both patients and caregivers. Most patients become symptomatic during childhood or adolescence (Maurer 2022). Despite the number of LTP and on-demand treatments available, attacks are not fully eliminated for some patients. Laryngeal oedema, which accounts for approximately 0.9% of all attacks, is a potentially life-threatening clinical manifestation of HAE that occurs in >50% of HAE patients at some point in their lives (Busse and Christiansen 2020).
The new medicinal product's placement in the treatment algorithm	First line treatment for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.
Patient population *Description, incidence and prevalence of the patient population covered by the relevant indication* in Norway, including references.* *Number of Norwegian patients assumed to be relevant for new method* ** The entire patient group covered by the indication in question is to be described*	In Norway there is an estimated prevalence of around 200 patients. There are approximately 150 patients being treated for HAE in Norway, and of these, 50-60 patients are eligible for preventive treatment. (The Norwegian Medicines Agency 2024)

7 Comparability to other medicinal products and inclusion in tender

Are there existing procurements or tenders in the therapeutic area?	Yes, LIS : 2599a HAE sykdom
Are there other medicinal products with a similar mechanism of action and/or similar effect (for the same indication)?	Garadacimab is a first-in-class recombinant monoclonal antibody inhibiting factor XIIa (anti-FXIIa mAb). Garadacimab is expected to be approved with a similar indication as Takhzyro (lanadelumab).
Does the supplier consider the medicinal product to be comparable to other medicinal products?	Garadacimab has been studied in a similar patient population as Takhzyro (lanadelumab) and is expected to be approved with a similar indication. Through indirect treatment comparison, garadacimab demonstrate superior efficacy on certain outcome measures, compared to Takhzyro (lanadelumab).

8 Relevant clinical trials
(pivotal trial(s) and clinical studies relevant for establishing relative efficacy)

	Study 1	Study 2	Study 3
Study ID *Study name, NCT number, hyperlink*	NCT04656418, VANGUARD, CSL312_3001 https://clinicaltrials.gov/study/NCT04656418?intr=NCT04656418&rank=1	NCT03712228, CSL312_2001, https://clinicaltrials.gov/study/NCT03712228?intr=NCT03712228&rank=1	NCT03712228, CSL312_2001 OLE study
Study type and design	Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled.	Phase 2,multinational, multicenter, randomized, double-blind, placebo controlled.	Phase 2, multinational, multicenter, open-label study.
Objective	The objective of this study was to evaluate the efficacy and safety of garadacimab 200 mg once monthly vs placebo for prophylaxis to prevent HAE attacks in patients ≥12 years of age with HAE	The objective was to evaluate the efficacy and safety of garadacimab vs placebo for prophylaxis to prevent HAE attacks in patients (18–65 years) with HAE and to determine the optimal dose for further assessment in the pivotal Phase 3 trial.	Open label extension study of CSL312_2001 to evaluate long term efficacy and safety for garadacimab 200 or 600 mg once monthly.
Population *Important inclusion and exclusion criteria*	Patients (>12 years) with type 1 or 2 HAE recruited from 28 sites in 7 countries (N=65). Inclusion criteria: • Male or female aged ≥12 years • Diagnosis of HAE, confirmed by the following criteria: documented clinical history consistent with HAE, C1-INH functional activity <50% of normal (per patient medical record), and C4 antigen concentration below the lower limit of the reference range (per patient medical record) • Experienced ≥3 HAE attacks during the 3 months before screening (per	Patients (18-65 years) with type 1 or 2 HAE recruited from 12 sites in 4 countries (N=32)	Patients (≥12 years) with type 1 or 2 HAE recruited from 13 sites in 4 countries (N=36)
Intervention (n) *Dosage, dosing interval, duration of treatment*	On the first day of the treatment period (day 1), patients in both arms were treated with a 400 mg loading dose (two 200 mg SC injections). This was followed by 5 self- or caregiver-administered monthly doses of 200 mg garadacimab SC injections over the remaining treatment period.	Garadacimab 600 mg, garadacimab 200 mg or garadacimab 75 mg. On the first day of the administration period (day 1), patients were treated with an initial IV loading dose of garadacimab 300 mg, garadacimab 100 mg, garadacimab 40 mg, or placebo; this was followed up with SC doses of garadacimab 600 mg, garadacimab 200 mg, and garadacimab 75 mg respectively, on day 6 and every 4 weeks thereafter.	Open-label garadacimab 200 or 600 mg once monthly.patients were exposed to garadacimab for a maximum of 116·6 weeks (26·8 months). Patients were exposed for a median of 87·9 weeks (IQR 50·0–106·6) to garadacimab 200 mg once monthly and 44·1 weeks (24·1–56·1) to garadacimab 600 mg once monthly.
Comparator (n) *Dosage, dosing interval, duration of treatment*	Placebo	Placebo	Placebo
Endpoints *Primary, secondary and exploratory endpoints, including definition, measurement method and, if applicable, time of measurement*	Primary endpoints The primary endpoint was the investigator-assessed time-normalized number of HAE attacks with garadacimab 200 mg vs placebo during the 6-month treatment period (day 1 to day 182). Secondary endpoints Three secondary efficacy endpoints comparing garadacimab 200 mg with placebo were tested in the following hierarchical order: • Percentage reduction in the monthly number of HAE attacks from baseline to the end of the treatment period • Number of patients who were attack-free at the end of the treatment period • Percentage of patients rating therapy as "good" or better with the SGART at the end of the treatment period Additional secondary efficacy endpoints were: attack rate reductions compared with the run-in period (defined as ≥50%, ≥70%, ≥90%, or 100% reduction) and attack rates over prespecified timepoints (Month 1 to 3, Month 4 to 6, Month 1 to 6), number of attacks per month requiring rescue medication, and number of moderate or severe attacks per month. Exploratory efficacy analyses Time to first HAE attack was an additional prespecified exploratory efficacy endpoint. (Data on file 2022) Investigator-reported outcomes and PROs PROs analysed as exploratory endpoints included the AE-QoL questionnaire,	Primary efficacy endpoints The primary endpoint was the time-normalized number of HAE attacks per month with garadacimab (75 mg, 200 mg, or 600 mg) vs placebo during the treatment period. Secondary efficacy endpoints Secondary efficacy endpoints comparing garadacimab (75 mg, 200 mg, or 600 mg) vs placebo over the treatment period were: • Proportion of patients who responded to garadacimab (75 mg, 200 mg, or 600 mg) or placebo (defined as ≥50% relative reduction in the number of HAE attacks vs the run-in period) • Proportion of patients who were attack-free • Proportion of mild, moderate, or severe HAE attacks • Overall number of HAE attacks • Proportion of patients requiring rescue medication Exploratory efficacy analyses There were two prespecified exploratory efficacy endpoints comparing garadacimab (75 mg, 200 mg, or 600 mg) and placebo over the treatment period: number of days per month patients experienced attacks and number of rescue medication uses per month. Investigator-reported outcomes and PROs Investigator-reported outcomes and PROs were analysed as exploratory endpoints. These included AE-QoL, WPAI:GH, SGART, and IGART.	Primary endpoint Monthly attack rate for patients receiving 200 mg or 600 mg garadacimab in CSL312_2001 in the intention-to-treat population
Relevant subgroup analyses *Description of any relevant subgroup analyses*	Subgroup analysis available as data on file.	N/A	N/A

	Study 1	Study 2	Study 3
Follow up time *If the study is ongoing, indicate the follow-up time for the data expected to be available for assessment by the Norwegian Medicines Agency as well as the expected/planned total follow-up time for the study*	6 months treatment period. At the end of the treatment period, patients either entered a 2-month follow-up period or entered the OLE study.	12 weeks treatment period. All patients entered an extension period of 44 weeks (and were followed up for an additional 14 weeks).	Please see "NCT03712228, CSL312_2001" Patients were exposed to garadacimab for a maximum of 116.6 weeks (26.8 months). Patients were exposed for a median of 87.9 weeks (IQR 50.0–106.6) to garadacimab 200 mg once monthly.
Time perspective results *Ongoing or completed study? Available and future data cut-offs*	Completed. Study duration: 27/01/21-07/06/22.	Completed. Start: 29/10/18 Completion: 15/10/21	Completed.
Publications *Title, author, journal, year. Expected date of publication*	Craig, T. J., Reshef, A., Li, H. H., Jacobs, J. S., Bernstein, J. A., Farkas, H., ... & Magerl, M. (2023). Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 401(10382), 1079-1090	Craig T, Magerl M, Levy DS, et al. Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2022;10328(399):945-955.	Craig TJ, Levy DS, Reshef A, Lumry WR, Martinez-Saguer I, Jacobs JS et al. Garadacimab for hereditary angioedema attack prevention: long-term efficacy, quality of life, and safety data from a phase 2, randomised, open-label extension study. Lancet Haematol. 2024;11(6):e436-e447

9 Ongoing and planned studies

Are there ongoing or planned studies for the medicinal product within the same indication that may provide further information in the future? *If yes, state the expected time perspective for data availability*	VANGUARD extension study, NCT04739059, Phase 3b, multinational, multicenter, open-label study. Completion (estimated): 11/25. Interim analysis: Reshef A, Hsu C, Katelaris CH, Li PH, Magerl M, Yamagami K et al. Long-term safety and efficacy of garadacimab for preventing hereditary angioedema attacks: phase 3 open-label extension study. Allergy. 2024 Oct 7. Doi: 10.1111/all.16351. Online ahead of print NCT05819775, Phase 3 paediatric study, multinational, multicenter, open-label study. Study completion date (estmated): 2026-11-11.
Are there ongoing or planned studies for the medicinal product for other indications?	No

10 Expected health economic documentation

Enter information about the expected health economic analysis

Type of health economic analysis *E.g. cost-per-QALY analysis or cost minimisation analysis* *(Justify the proposal)*	Cost utility analysis, using Takhzyro (lanadelumab) as comparator. Due to garadacimab demonstrating superior efficacy on certain outcome measures in the indirect treatment comparison, a cost utility analysis using Takhzyro (lanadelumab) as comparator is planned.
The patient population on which the health economic analysis is based, including any subgroups. *The main analysis (base case) shall include the entire patient population covered by the indication sought.*	Aligned with the patient population accroding to approved indication and the study population in pivotal study CSL312_3001, NCT04656418.
What type of documentation will form the basis for estimating relative efficacy? *(Direct or indirect evidence)*	Indirect evidence: Anchored MAIC to estimate the relative efficacy of garadacimab versus lanadelumab.
What type of documentation will form the basis for health-related quality of life data?	In the base case scenario, utilities from published studies most relevant for the Norwegian patient population that adheres to the Norwegian requirements will be used.
Expected pharmaceutical budget impact per year, in the 5-year period following a potential approval	To be described in the submitted dossier.

11 Suitable for FINOSE?

Can the method be appropriate for assessment through FINOSE (yes/no) *If no, why not?*	No, Nordic countries essentially follow the same international treatment guidelines, but available treatments vary due to different reimbursement landscapes. Hence, the use of different treatments in clinical practice varies significantly between Nordic markets. In addition, as HILA in Finland is not part of the JNHB collaboration garadacimab would not be assessed in Finland and therefore not a suitable candidate for the JNHB process.

12 Other relevant information

Disclose other aspects that Nye metoder should be aware of.

Have you been in contact with clinicians at Norwegian health trusts about this medicinal product/ indication? Yes/no *If so, who have you been in contact with and what have been their contribution?* *(Relevant information in connection with the recruitment of experts in the field at Nye metoder)*	No
Are there specific circumstances related to the medicinal product implying that a plain discount may not be appropriate for fulfilment of the priority criteria (yes/no)? *If yes, a separate form must be completed and sent nyelegemidler@sykehusinnkjop.no at the same time as documentation is sent to the Norwegian Medicines Agency for a health technology assessment.* *Information and form:* https://www.sykehusinnkjop.no/om-oss/informasjon-og-opplering/	No
Any other relevant information?	N/A