EU Risk Management Plan

for

Garadacimab

RMP version to be assessed as part of this application:

RMP Version number:	1.0
Data lock point for this RMP:	16 June 2023
Date of final sign off:	20 December 2024
Rationale for submitting an updated RMP:	Not applicable (for initial MAA submission)
Summary of significant changes in this RMP:	Not applicable (for initial MAA submission)
QPPV name:	Dr. med. Juergen Zorn
QPPV signature:	_____

Abbreviations

Term / Abbreviation	Description
C1INH	C1 esterase inhibitor
EPAR	European Public Assessment Report
EU	European Union
HAE	Hereditary angioedema
HAE-C1INH	Hereditary angioedema due to C1 esterase Inhibitor deficiency or dysfunction
HAE-nC1INH	Hereditary angioedema with normal C1 inhibitor level
HSR	Hypersensitivity reaction
IV	Intravenous
mAb	Monoclonal antibody
RMP	Risk management plan
SC	Subcutaneous
SmPC	Summary of product characteristics
US	United States

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Part I: Product(s) Overview

Table Part I-1: Product(s) Overview

Active substance(s) (INN or common name)	Factor XIIa Inhibitor Monoclonal Antibody (CSL Product Code: CSL312) INN: garadacimab
Pharmacotherapeutic group(s) (ATC Code)	ATC Code: B06AC07
Name of Marketing Authorisation Applicant	CSL Behring GmbH
Medicinal products to which this RMP refers	Factor XIIa Inhibitor Monoclonal Antibody - garadacimab (CSL Product Code: CSL312)
Invented name(s) in the European Economic Area (EEA)	Andembry®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Factor XIIa Inhibitor Monoclonal Antibody. Garadacimab is a fully human IgG4 mAb which binds to FXIIa. Garadacimab has a structure typical of IgG4 mAbs consisting of 2 heavy and 2 light chains, joined by disulfide bonds. Garadacimab has a molecular weight of ~ 148.2 kDa.
	Summary of mode of action: Garadacimab is a fully human mAb which selectively and effectively inhibits FXIIa. FXIIa is responsible for the initiation of the contact system and its inhibition via garadacimab thus limits the excessive production of the inflammatory vasoactive bradykinin which is central to the pathogenesis of angioedema attacks in patients with HAE.
	Important information about its composition: Garadacimab is preservative-free, 0.2 µm sterile filtered, liquid solution formulated for SC injection. The active substance, Factor XIIa Inhibitor Monoclonal Antibody (garadacimab), expressed in Chinese hamster ovary cells is formulated in buffer containing the following stabilisers: L-Histidine, L-Arginine, L-Proline and Polysorbate 80. It does not contain novel excipients or excipients of animal or human origin. The excipients have been approved for use in the formulation of currently marketed

	plasma-derived and recombinant factor drug products and are safe.
Hyperlink to the Product Information	Andembry EU Product Information [link]
Indication(s) in the EEA	Current: Garadacimab is indicated for routine prevention of recurrent attacks of HAE in adult and adolescent patients aged 12 years and older.
	Proposed: Not applicable
Dosage in the EEA	Current: A fixed monthly dose of 200 mg garadacimab given SC following a loading dose administered as 2 × 200 mg SC injections.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection in needle safety device or auto-injector. One unit contains 200 mg of garadacimab in 1.2 mL of solution.
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	Yes

ATC = anatomical therapeutic chemical; EEA = European economic area; EU = European Union; FXIIa = activated human coagulation factor XII; HAE = hereditary angiooedema; Ig = immunoglobulin; INN = International nonproprietary name; mAb = monoclonal antibody; RMP = risk management plan; SC = subcutaneous

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population

HAE indication

Garadacimab is being developed for routine prevention of recurrent attacks of hereditary angioedema (HAE). HAE is a rare autosomal dominant disease characterised by recurrent, unpredictable, localised and self-limiting swelling of the subcutaneous (SC) and / or submucosal tissue, due to a temporary increase in vascular permeability (Bork et al, 2006; Reshef et al, 2024).

HAE is classified into:

- **HAE due to C1 esterase inhibitor (HAE-C1INH) deficiency or dysfunction**
  - HAE Type I: Low plasma levels of C1INH-protein
  - HAE Type II: Normal or elevated plasma levels of dysfunctional C1INH protein
- **HAE with normal C1INH levels** (respectively, identified as type **HAE-nC1INH**) which is further classified into:
  - HAE-FXII, due to FXII mutation
  - HAE-PLG: Due to plasminogen mutation
  - HAE-KNG1: Due to kininogen-1 mutation
  - HAE-ANGPT1: Due to angiopoietin-1 mutation
  - HAE-MYOF: Due to myoferlin mutation
  - HAE-HS3ST6: Due to heparan sulfate-glucosamine 3-O-sulfotransferase 6 mutation
  - HAE-UNK: Due to unknown mutation

Incidence / Prevalence:

HAE affects between 1 in 10,000 and 1 in 50,000 people, with no clear ethnic variation (Gompels et al, 2005; Maurer et al, 2022; Riedl, 2012). Specifically utilising European Union (EU) data sources, a systematic review and meta-analysis estimated prevalence at 1.1 to

1.6 per 100,000 persons across all ages (1 per 63,000 to 91,000 persons) (Aygören-Pürsün et al, 2018) Type 1 HAE is the most common form, accounting for about 85% of HAE cases and Type 2 accounts for approximately 15% of HAE cases (Zuraw et al, 2010). Prevalence estimates of HAE-nC1INH are extremely limited. A study conducted in Germany estimated the prevalence as 0.10 per 10,000 persons (Bork et al, 2015). An explanation for this calculation was not provided and is relatively high given a previous study that estimated that HAE-nC1INH was extremely rare and was no more than 10 to 20% of the overall HAE-C1INH prevalence (Zuraw et al, 2012).

Demographics of the population in the proposed indication and risk factors for the disease:

The mean age at the onset of initial symptoms of HAE is 8 to 12 years (Bork et al, 2006; Farkas, 2007). Patients with early onset of clinical symptoms are affected more severely than those with late onset (Bork et al, 2006). Between 50 and 75% of patients had their first attack by the age of 12 years. Almost 40% had onset of their symptoms before the age of 5 years, and 75% before the age of 15 years (Bork et al, 2006; Gompels et al, 2005). There is no reported bias in the prevalence of the disease in different ethnic groups (Gompels et al, 2005). Female patients are usually more severely affected by HAE than men (Caballero, 2012), although there is no apparent difference in HAE prevalence by gender (Bernstein, 2018).

The main existing treatment options: Management options for HAE can include on-demand therapy (acute treatment) for individual attacks, long-term prevention of attacks, short-term prevention prior to potentially attack-triggering events (ie, medical, surgical, or dental procedures), or combinations of these strategies (Maurer et al, 2022).

The treatment of choice in case of an acute attack of HAE is the rapid replacement of the functionally missing plasma protein by intravenous (IV) administration of C1INH concentrate in countries where C1INH is available or, less preferentially, fresh frozen plasma or native plasma as a source of C1 inhibitor if C1INH is not available. Over the past 25 years, studies have confirmed the efficacy of plasma C1INH as replacement therapy for acute attacks of HAE. Symptom relief is usually seen within 30 to 60 minutes of IV administration of C1INH. In addition to Berinert IV, the C1INH concentrates Cinryze (C1INH [Human]) and Ruconest (C1INH [Recombinant]) and the bradykinin receptor antagonist Firazyr (icatibant) are authorised for the acute treatment of HAE attacks.

First line medications for routine prophylaxis against angioedema attacks include Berinert SC, berolstrat and lanadelumab, a monoclonal antibody (mAb) targeting plasma

kallikrein. Cinryze (C1INH [human]) is indicated for routine prophylaxis against angioedema attacks, but only when other prophylactic options have failed.

Prior to the availability of these targeted HAE therapies, anabolic steroids (androgens) such as danazol, oxandrolone, and stanozolol were commonly prescribed for treating HAE patients, mainly for prophylaxis of attacks. While anabolic steroids have been shown to be useful, they are not well tolerated by many women, are directly linked to liver toxicity, and cause an increase in cholesterol levels. In addition, these drugs should not be used to treat children. As typical anti-inflammatory drugs are not effective and are available in a limited number of countries in the EU, they are not routinely used. Antifibrinolytics are not recommended as such, but some patients may find them helpful (Maurer et al, 2022).

In addition to routine prophylaxis, short-term prophylaxis, or situational prophylaxis, is recommended before exposure situations where there is an increased risk of HAE attack. For example, HAE attacks may arise shortly after surgical procedures, dental procedures, other medical interventions, or other HAE attack-inducing events. Using IV plasma-derived C1INH as short-term prophylaxis before any medical, dental, or other HAE attack-inducing procedure / event is recommended as first-line treatment. Recombinant C1INH may also be considered if IV C1INH is not available. The recommended second-line short-term prophylaxis treatment is fresh frozen plasma although it is deemed to be less safe compared to plasma derived C1INH (Maurer et al, 2022).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

HAE is characterised by recurrent attacks of non-pruritic angioedema, affecting the SC and submucosal tissue, lower abdominal organs, and upper airway, with the most frequent sites of swelling being the skin, abdomen, and larynx (Bernstein, 2018). In a study conducted out of Germany, 209 patients with clinically symptomatic HAE were asked about their condition. Authors found that 201 out of the 209 patients experienced recurrent skin swelling, and out of those 201 patients with skin swelling, 97% experienced swelling of the abdomen and 54% experienced swelling of the larynx (Bork et al, 2006). Most individuals with HAE are symptom-free until the onset of symptoms within the first decade of life after which they experience attacks for the remainder of their lives. Symptoms may worsen around puberty, but the pathophysiology of HAE is consistent across age groups (Bernstein, 2018). Some individuals may experience symptom-free intervals which are part of the natural course of

their disease, while others may use long-term prophylaxis to achieve symptom-free years (Bork et al, 2006).

HAE symptoms usually develop gradually over several hours, increase slowly for 12 to 36 hours, and subside after 2 to 5 days (Riedl, 2012). Attack onset is unpredictable, and episodes vary in frequency, severity, and anatomical location among patients with HAE.

HAE symptoms are often functionally disabling, painful, and disfiguring, and upper airway attacks can be life-threatening because of the risk of asphyxiation (Bernstein, 2018; Riedl, 2012). HAE has a profound effect on the quality of life of affected patients and negatively affects educational and professional endeavours, social activities, and mental health (Riedl, 2012). One survey of individuals in the United States (US) with HAE found that 72% of those with HAE types 1 or 2 and 76% of those with HAE-nC1INH reported that HAE had a significant impact on their quality of life. If left untreated, 86% of those with HAE types 1 or 2 reported that at minimum 75% of their attacks were severe enough to negatively impact their quality of life (Banerji et al, 2015).

While the age of HAE symptom onset tends to occur within the first decade of life, the age at which HAE is officially diagnosed is often delayed. This delay in diagnosis is multifactorial, driven by lack of awareness by both patients and practitioners due to the rareness of HAE and exacerbated by the intermittent nature of the disorder (Lumry et al, 2020). HAE symptoms are also commonly mistaken for other ailments like allergic reactions, irritable bowel syndrome, or appendicitis (Banerji et al, 2015). Additionally, HAE must be diagnosed by evaluating both clinical symptoms and family history and confirmed using laboratory testing. An individual without a family history of HAE can still present with a spontaneous C1INH mutation, making it even more challenging for clinicians to diagnose in young children (Bernstein, 2018). One US-based survey study in HAE patients showed a median delay in diagnosis of 8 years, with longer delay in diagnosis in those with earlier onset of symptoms. This same study also demonstrated that earlier symptom onset was correlated with increased HAE severity as well as increased number of attacks per year and hospital admissions (Christiansen et al, 2016). The delay in diagnosis of HAE is important because this leaves individuals vulnerable to attack and even death, given that most deaths due to HAE are in those who are undiagnosed (Bernstein, 2018).

All affected individuals are at risk for a life-threatening episode of laryngeal angioedema, which continues to be a source of fatalities due to asphyxiation. Death in HAE due to asphyxiation is a serious risk in patients with previously undiagnosed HAE and untreated

patients. Mortality, secondary to laryngeal oedema and asphyxiation, has been reported in up to 30% of patients with previously undiagnosed HAE (Craig et al, 2009). However, the risk of mortality is greatly reduced with more appropriate diagnosis and use of available treatments (Agostoni et al, 2004).

Important co-morbidities:

HAE negatively impacts a patient's daily life, psychosocial health, and productivity both during times of attack and during times of remission (Aygören-Pürsün et al, 2018). HAE is a huge burden on patients who live in fear of an attack, which impacts their mental health. In addition to the attacks themselves, HAE patients might experience HAE-related deaths within their family, they might feel overwhelmed by family planning decisions, they might experience unnecessary medical procedures due to misdiagnosis, and they might experience restrictions of daily-activities or work responsibilities. All these many factors contribute to the burden of HAE on patients and are associated with depression and anxiety in this population (Zarnowski et al, 2021). Anxiety and depression have been reported among individuals with HAE. In one multinational patient survey of HAE patients, results from a mental health composite score (12-Item Short-Form Health Survey) showed that individuals with HAE had a lower score, indicating poorer mental health, compared to the score normalised to the general population. (Mendivil et al, 2021). In a separate study out of Germany, individuals with HAE who were on long-term prophylaxis experienced lower levels of anxiety and depression, as well as better quality of life, compared to those using on-demand treatment only (Zarnowski et al, 2021).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Single-dose Toxicity	Single-dose toxicity studies were not performed for garadacimab (CSL312) and for excipient L-proline
Repeat-dose Toxicity In Study No. APQ0056 CD-1 mice received CSL312, by IV (bolus; doses of 3, 10, 30 and 100 mg/kg) or SC (doses of 60 and 200 mg/kg) administration over an 8-day period (dosed on Days 1, 4 and 8). There were no findings at any dose level tested, therefore the no observed adverse effect level (NOAEL) is 100 mg/kg/occasion IV and 200 mg/kg/occasion SC. In Study No. APQ0061 CD-1 mice were treated with CSL312 IV (bolus; doses of 3, 10, 30 and 100 mg/kg) or SC (doses of 60 and 200 mg/kg) for 4 weeks (dosed on Days 1, 4, 8, 11, 15, 18, 22, 25 and 29) followed by an 8-week recovery period. Treatment-related clinical signs (eg, oedema formation, decreased activity, shallow breathing) and mortality after repeat dosing in the 3 mg/kg IV group (and partially in the 10 and 30 mg/kg IV groups) occurred due to an immunological (ie, anaphylactic) reaction toward the heterologous human protein. There were no other findings of toxicological significance at the dose levels tested (3, 10, 30, and 100 mg/kg/occasion IV and 60 and 200 mg/kg/occasion SC). No NOAEL could be established after IV administration due to the early termination of the low IV group (3 mg/kg/day). The NOAEL of 200 mg/kg was established after SC administration. In Study No. TOM 16-02 the adverse events observed during the GLP study APQ0061 was further characterised. Repeated IV bolus administration of 3 mg/kg CSL312 over 4 weeks (dosed on Days 3, 7, 10, 14, 17, 21, 24, 28) to mice confirmed an immunological (ie, anaphylactic) reaction to treatment	In repeat-dose studies of CSL312 in 2 species (mouse, cynomolgus monkey), there are no significant safety findings at multiple times the human therapeutic dose. No toxicity in humans is expected. Since immunological reactions are principally expected in animals after repeat dosing of heterologous proteins, these data are considered not predictive of a potential of antibody formation in humans and thus for the clinical situation, which is in line with the ICH S6(R1) guideline (ICH S6(R1), 2011).

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
with the heterologous human antibodies as the cause of the adverse effects observed in GLP study APQ0061. In Study No. APQ0055 cynomolgus monkeys were administered IV (bolus; doses of 3, 10, 30, and 100 mg/kg) and SC (doses of 60 and 200 mg/kg) for 8 days. There were no other findings of toxicological significance at any dose level tested (up to 100 mg/kg/occasion IV and 200 mg/kg/occasion SC). The NOAEL is 100 mg/kg/occasion IV and 200 mg/kg/occasion SC. In Study No. APQ0058, cynomolgus monkeys were treated with CSL312 IV (bolus; doses of 3, 10, 30 and 100 mg/kg) and SC (doses of 60 and 200 mg/kg) for 5 weeks followed by an 8-week recovery period. Treatment-related prolongation of aPTT irrespective of the route of administration was consistent with the expected pharmacological response to treatment with CSL312. There were no other findings of toxicological significance at any dose level tested. The NOAEL is 100 mg/kg/occasion IV and 200 mg/kg/occasion SC. In Study No. TH43GT cynomolgus monkeys were treated with CSL312 IV (bolus; doses of 10, 30 and 100 mg/kg) and SC (doses of 60 and 200 mg/kg) for 26 weeks with a 13-week interim phase followed by an 8-week recovery period. Two animals in the main phase of the study were euthanised for welfare reasons. The clinical observations and overall pattern of endpoints of these 2 animals were consistent with adverse immunogenic type reactions to CSL312 treatment. Pathological changes in any other treated animals were confined to the injection sites and consisted of local inflammatory responses and lymphoid aggregates, which were considered to represent a mild local irritant effect of the test item. All these differences from control showed at least partial recovery after the 8-week recovery period. Therefore, under the conditions of this study and considering the early termination of the 2 animals that received 100 mg/kg/occasion (IV) or 200 mg/kg/occasion (SC), a total of 27 weekly repeated	

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
doses of CSL312 administered via IV (bolus) or SC injection to cynomolgus monkeys resulted in a NOAEL of 30 mg/kg/occasion (IV) and 60 mg/kg/occasion (SC), respectively. About the interim phase evaluations (ie, analyses following a total of 14 weekly repeated doses of CSL312) a NOAEL of 100 g/kg/occasion (IV) and 200 mg/kg/occasion (SC), respectively could be applied. In a 5-day (Study No. 925/034) and a 28-day (Study No. 925/035) repeat-dose toxicity study in Sprague Dawley rats, daily IV dosing of L-proline up to the maximum daily dose that could be infused showed no overt toxicity. The NOAEL was the highest dose tested (1449 mg/kg/day). In a 7-day (Study No. 668316) and 28-day (Study No. 668321) repeat-dose toxicity study in beagle dogs, daily IV dosing of L-proline up to the maximum doses that could be infused showed no overt toxicity. The NOAEL was the highest dose tested (4350 mg/kg/day).	In repeat-dose studies of L-proline in 2 species (rat, dog), there were no significant safety findings at multiple times the human therapeutic dose. No toxicity in humans is expected.
Reproductive and Developmental Toxicity In a female fertility and early embryonic development to implantation study (Study No. 8408860) no CSL312- related effects on mating, fecundity, or fertility indices were observed. No effects on maternal reproductive parameters or embryo survival were noted. Therefore, the NOAEL for maternal and fetal toxicity and for maternal and developmental toxicity and female fertility is 100 mg/kg/dose. In a male fertility and early embryonic development to implantation study (Study No. 8399537), no CSL312-related effects on mating, fertility, or fecundity indices, and no effects on sperm assessment were observed. There were 6 unscheduled deaths out of 75 treated animals that were most likely related to an immunologic reaction to the human heterologous protein. Therefore, the NOAELs for both the paternal and the mating, fertility, or fecundity is 100 mg/kg/occasion.	No CSL312-related toxicologically relevant effects were observed in any reproductive toxicity studies at dose levels up to 100 mg/kg IV and SC.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
In an embryo-fetal development study in rabbits (Study No. VK47BJ), no effect of maternal treatment with CSL312 on the mean numbers of implantations, pre- or post-implantation losses, litter size, sex ratio, or on placental, fetal and litter weights or fetal pathology findings. Therefore, the NOAEL for maternal and fetal toxicity is 100 mg/kg/occasion. In a pre- and postnatal development study in rabbits (Study No. 8410864), no CSL312-related toxicity was observed in the parental or F1 generation. The NOAEL for maternal and fetal toxicity and for developmental, neurobehavioral, and reproductive performance in the F1 generation is 100 mg/kg/dose IV / SC. A rat teratogenicity study using L-proline alone (Study No. AA30034) provided evidence for the lack of maternal toxicity, teratogenicity and embryotoxicity at the tested dose of 1449 mg L-proline/kg/day. This dose represents the maximum applicable dose in this model, and a NOEL.	No L-proline-related toxicologically relevant effects were observed in development toxicity study at dose levels up to 1449 mg/kg IV. Only teratogenicity (segment II) data for L-proline have been generated because the amino acid L-proline is endogenously bioavailable in humans and is normally taken up by the diet, due to which exposure to L-proline through CSL312 would only slightly increase the total daily dose of L-proline. Therefore, it is highly unlikely that L-proline taken up via CSL312 would result in systemic effects including reproductive toxicity / developmental toxicity. Furthermore, in the two 28-day toxicity studies in rats, there were no treatment-related histopathological findings in male and female reproductive tissues treated at the highest dose and sacrificed on the last day of the studies.
Local Tolerance In the local tolerance study in rabbits (Study No. 37761), CSL312 administered SC at 100 and 170 mg/ml did not reveal CSL312-related changes at the injection sites or PK differences. CSL312 was well tolerated in mice and monkeys in the repeated-dose toxicity studies. Local tolerance studies were not performed for L-proline.	Based on local tolerance studies in rabbits, CSL312 is considered well tolerated following the intended clinical SC administration.
Genotoxicity No non-clinical genotoxicity studies have been conducted for CSL312.	The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed (ICH S6(R1)). Moreover, the administration of large quantities of peptides / proteins may yield uninterpretable results.

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
L-Proline did not show mutagenic or genotoxic effects in a battery of validated in vitro and in vivo assays (Study Nos 22196, 49196, CLE 1554/3-D5140, CLE 1554/4-D5140).	There is no evidence to suggest that genotoxicity or mutagenicity can be induced by CSL312 since there is no direct interaction with deoxyribonucleic acid (DNA) to anticipate any DNA damage or interaction with DNA binding proteins. There is no evidence to suggest that genotoxicity or mutagenicity can be induced by L-proline.
Carcinogenicity No carcinogenicity studies have been conducted for CSL312. A detailed carcinogenicity assessment concluded that: 1) No carcinogenic potential of the product class (inhibition of FXIIa) was previously demonstrated, 2) Structure-activity relationship suggests no carcinogenic risk for CSL312 and its excipients, 3) No genotoxicity for a biotechnology-derived pharmaceutical such as CSL312 is expected, 4) No evidence of pre-neoplastic or neoplastic lesions could be found in repeated dose toxicity studies and, 5) Long-term tissue retention of CSL312 does not occur and no local tissue reactions were observed during non-clinical studies. No carcinogenicity studies were conducted for L-proline.	As per standard ICH Guideline S6(R1), carcinogenicity studies are generally inappropriate for the evaluation of biotechnology-derived pharmaceuticals. Based on a weight of evidence approach, CSL312 is not expected to have carcinogenic potential when administered to patients (Carcinogenicity Risk Assessment of CSL312 - REP-008854). Based on a weight of evidence approach (no mutagenic or genotoxic effects demonstrated in genotoxicity studies with L-proline, physiological presence, high oral NOAEL), L-proline is not expected to have carcinogenic potential when administered to patients (Carcinogenicity Risk Assessment on Excipients of CSL312-ST2020CSL-001).

aPTT = activated partial thromboplastin time; DNA = deoxyribonucleic acid; FXIIa = activated human coagulation factor XII; GLP = good laboratory practice; IV = intravenous; NOAEL = no observed adverse effect level; NOEL = no observed effect level; PK = pharmacokinetic; SC = subcutaneous

Safety pharmacology

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Safety pharmacology No adverse treatment-related effects of CSL312 on respiratory parameters were observed in the respiratory safety pharmacology study in mice (Study No. APQ0056) or on cardiovascular (electrocardiogram (ECG) and blood pressure), respiratory (respiration rate) and central nervous system safety readouts integrated in the repeat-dose toxicity studies in mice and cynomolgus monkeys (Study Nos. APQ0061, APQ0058, TH43GT). The effect of L-proline on the CNS (Irwin test) was evaluated in rats with daily IV application for 5 days (Study No. 1657/ZLB/02). L-proline did not significantly affect the behaviour of animals during and after infusion at all doses up to 1449 mg/kg tested. In an exploratory acute neurotoxicity study (Study No. PSR 08/06), female rats were injected SC with 2000 mg L-proline/kg or IP with 2000 and 4000 mg L-proline/kg. No clinical signs including signs of acute neurotoxicity were found. No clinical signs, including neurological effects and signs of seizures, were found after SC injection of 2000 mg L-proline/kg which resulted in maximum plasma concentrations of 12 mmol/L (Study No. PSR 03/07). A Morris water maze task neurotoxicity study in juvenile rats (Study Nos. PSR 01/07, ZLB 06_006) did not induce acute neurotoxic signs or brain development at daily SC doses up to 4000 mg/kg.	Based on nonclinical data, no safety relevant adverse effects on cardiovascular, respiratory, and neurological parameters are expected from nonclinical testing for CSL312 in human use. Based on nonclinical data, no safety relevant adverse effects on cardiovascular, respiratory, and neurological parameters are expected for L-proline in human use.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Mechanisms for drug interactions The potential effects of a combination of CSL312 and different classes of anticoagulant / anti-platelet drugs on bleeding were investigated in rodent models of hemostasis. A murine tail-tip bleeding model and a rabbit organ-bleeding model were used in this context. Specifically, potential effects on hemostasis were evaluated using a combination of CSL312 and Acetylsalicylic acid in mice (Study No. SBM 22-05). Similarly, CSL312 in combination with clopidogrel was tested in rabbits (Study No. ASK 22-03). For heparin-based medications, combination studies with CSL312 were performed in mice and rabbits for low molecular weight heparin (Study No. SBM 19-01 and VTK 19-01 respectively) and in rabbits for UFH (Study No. ASK 22-01). For DOACs eg, Rivaroxaban, a combination study with CSL312 was performed in rabbits (Study No. ASK 21-02). Time to hemostasis and volume of blood lost following the resection/organ injury was measured. In all such studies performed so far, a combination treatment with CSL312 did not result in a further increase in bleeding compared to treatment with the medication alone.	Since the metabolism, distribution, and elimination of mAbs are not mediated by cytochrome P450 (CYP450) or cell membrane transporters, mAbs are not expected to compete directly with chemically derived drugs. Therefore, no drug interactions are expected for CSL312 treatment. To date, no interactions of CSL312 with other medications are known. Results from nonclinical studies in rabbit and mouse models following administration of 10 mg/kg CSL312 in combination with DOACs, low-molecular-weight heparin and UFH did not show any risk of exacerbation of bleeding. The non-essential amino acid L-proline is permanently present in the blood and has been used in high doses as component of solutions for parenteral nutrition. Pharmacodynamic interactions with drugs have not been reported in the literature and based on the biotransformation routes, are not to be expected at the doses applied with CSL312.
Studies in juvenile animals No non-clinical studies with juvenile animals were conducted with CSL312. Study in juvenile rats (Study Nos. PSR 03/07, SR 01/07 and ZLB06_006) confirmed a good PK profile and safety of high L-proline in juvenile animals in general and especially during brain development.	Following an appropriate Weight of Evidence analysis performed in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline S11, juvenile studies were omitted. No relevant safety signals that could have any impact on the development in children were identified so far in the nonclinical program for CSL312. Results from non-clinical studies specifically investigating the excipient L-proline did not reveal risks compliant with the definitions for important identified risk or important potential risk.

CNS = central nervous system; CYP450 = cytochrome P450; DOAC = direct oral anticoagulant; ECG = electrocardiogram; IP = intraperitoneal; IV = intravenous; mAb = monoclonal antibody; PK = pharmacokinetic; SC = subcutaneous; UFH = unfractionated heparin

Other toxicity-related information or data

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Tissue Cross Reactivity In vitro cross-reactivity data (Study No. APQ0057) showed that specific staining in cynomolgus monkeys was generally predictive of staining in human tissues.	Since in vivo physiological barriers are present (cell membrane, blood brain barrier, blood testes barrier, etc.) which limit the drug access to specific tissues, no risk for off-target effects of CSL312 is expected. Non-clinical data showed that IV or SC doses of CSL312 were well tolerated in monkeys in repeat-dose studies and did not result in any drug-related clinical and macroscopic or histopathological findings in the organs assessed.

IV = intravenous; SC = subcutaneous

Based on the nonclinical data available, there are no safety concerns regarding the use of garadacimab (CSL312) within the intended clinical indication. No additional, nonclinical testing relevant to the indication or population is deemed necessary.

Part II: Module SIII - Clinical trial exposure

Clinical trial exposure of all studies on garadacimab to date (1001, 1003, 1004, 2001, COVID-19, 2002, 3001, 3002) are included in this section, including the completed study on the COVID-19 indication and the ongoing phase 2 study in the Idiopathic pulmonary fibrosis indication (2002). Additionally, garadacimab is also currently being investigated by the SC route at a concentration of 100 mg/mL for the preventive treatment of HAE in pediatric subjects (study 3003). As of the data-cut off for this risk management plan (RMP), the pediatric study is ongoing with enrolment activities. At the data lock point of this RMP, there are no exposure data available for study 3003 and no safety concerns are identified.

Table SIII-1: Duration of exposure

Cumulative for All Indications (Person-Time)		
Duration of Exposure	**Patients / Subjects**	**Person-Time (Months)**
< 1 month	58	45.14
1 to < 3 months	198	531.38
3 to < 6 months	45	194.92
6 to < 12 months	10	88.05
≥ 12 months	155	3987.84
Total person-time	**446**	**4847.34**

CCI [redacted]

HAE Indication		
Duration of Exposure	**Patients / Subjects**	**Person-Time (months)**
< 1 month	2	1.77
1 to < 3 months	184	507.01
3 to < 6 months	22	86.06
6 to < 12 months	10	88.05
≥ 12 months	155	3987.84
Total person-time for indication	**373**	**4670.75**
COVID-19 Indication		
Duration of Exposure	**Patients / Subjects**	**Person-Time (months)**
< 1 month	52	41.59
1 to < 3 months	6	6.77
3 to < 6 months	0	0
6 to < 12 months	0	0
≥ 12 months	0	0
Total person-time for indication	**58**	**48.36**
IPF Indication		
Duration of Exposure	**Patients / Subjects**	**Person-Time (months)**
< 1 month	4	1.77
1 to < 3 months	8	17.61
3 to < 6 months	23	108.85
6 to < 12 months	0	0
≥ 12 months	0	0
Total person-time for indication	**35**	**128.23**

HAE = hereditary angioedema; IPF = idiopathic pulmonary fibrosis
(1) Due to the fact that CSL312_2002 study is ongoing and double-blinded, exposure summary results for CSL312 subjects are just estimated values based on the 1:1 randomisation ratio (Garadacimab vs. Placebo) of the study.

Table SIII-2: Age group and sex

Age Group	Patients / Subjects		Person-Time	
	M	**F**	**M**	**F**
Premature infants	0	0	0	0

CCI [redacted]

Age Group	Patients / Subjects		Person-Time	
Newborns (0-27 days)	0	0	0	0
Infants (1-23 months)	0	0	0	0
Children (2-11 years)	0	0	0	0
Adolescents (12-17 years)	5	6	81.74	114.00
Adults (18-64 years)	186	195	1760.79	2468.34
Elderly (65-75 years)	28	21	179.98	189.73
Very Elderly (>75 years)	13	12	21.45	31.31
Total	**232**	**234**	**2043.96**	**2803.38**
HAE Indication				
Age Group	**Patients / Subjects**		**Person Time**	
	M	**F**	**M**	**F**
Premature infants	0	0	0	0
Newborns (0-27 days)	0	0	0	0
Infants (1-23 months)	0	0	0	0
Children (2-11 years)	0	0	0	0
Adolescents (12-17 years)	5	6	81.74	114.00
Adults (18-64 years)	186	195	1760.79	2468.34
Elderly (65-75 years)	28	21	179.98	189.73
Very Elderly (>75 years)	13	12	21.45	31.31
Total	**232**	**234**	**2043.96**	**2803.38**
COVID-19 Indication				
Age Group	**Patients / Subjects**		**Person Time**	
Premature infants	**M**	**F**	**M**	**F**
Newborns (0-27 days)	0	0	0	0
Infants (1-23 months)	0	0	0	0
Children (2-11 years)	0	0	0	0
Adolescents (12-17 years)	0	0	0	0
Adults (18-64 years)	0	0	0	0
Elderly (65-75 years)	13	17	12.06	15.77
Very Elderly (>75 years)	10	5	7.00	4.73
Total	**31**	**27**	**25.33**	**23.03**

CCI [redacted]

Age Group	Patients / Subjects		Person-Time	
IPF Indication				
Age Group (1)	**Patients / Subjects**		**Person Time**	
	M	**F**	**M**	**F**
Premature infants	0	0	0	0
Newborns (0-27 days)	0	0	0	0
Infants (1-23 months)	0	0	0	0
Children (2-11 years)	0	0	0	0
Adolescents (12-17 years)	0	0	0	0
Adults (18-64 years)	2	0	10.18	0
Elderly (65-75 years)	11	10	38.01	36.07
Very Elderly (>75 years)	5	7	15.18	28.78
Total	**18**	**17**	**63.38**	**64.85**

HAE = hereditary angioedema; IPF = idiopathic pulmonary fibrosis
(1) Due to the fact that CSL312_2002 study is ongoing and double-blinded, exposure summary results for CSL312 subjects are just estimated values based on the 1:1 randomisation ratio (CSL312 vs. Placebo) of the study.

Table SIII-3: Dose

Cumulative for All Indications		
Dose of Exposure	**Patients / Subjects**	**Person-Time (Months)**
0.1 mg/kg CSL312 IV	4	12.65
0.3 mg/kg CSL312 IV	4	12.81
1 mg/kg CSL312 IV	4	11.43
1 mg/kg CSL312 SC	4	11.24
3 mg/kg CSL312 IV	8	22.47
3 mg/kg CSL312 SC	4	11.76
10 mg/kg CSL312 IV	8	21.98
10 mg/kg CSL312 SC	4	11.24
200 mg CSL312 SC single dose	157	433.38
200 mg CSL312 q4wk SC	166	3754.25
300 mg CSL312 IV single dose	35	11.43
400 mg CSL312 q2wk SC	6	16.53
400 mg CSL312 q4wk SC	3	42.45
600 mg CSL312 SC single dose	4	11.01

600 mg CSL312 q4wk SC	24	270.88
600 mg CSL312 SC, week 2, 4, 10	31	116.80
75 mg CSL312 q4wk SC	9	26.68
300 mg CSL312 IV loading dose	11	4.96
700 mg CSL312 single dose	58	48.36
Total (1)	**466**	**4847.34**
HAE Indication		
Dose of Exposure	**Patients / Subjects**	**Person Time (months)**
0.1 mg/kg CSL312 IV	4	12.65
0.3 mg/kg CSL312 IV	4	12.81
1 mg/kg CSL312 IV	4	11.43
1 mg/kg CSL312 SC	4	11.24
3 mg/kg CSL312 IV	8	22.47
3 mg/kg CSL312 SC	4	11.76
10 mg/kg CSL312 IV	8	21.98
10 mg/kg CSL312 SC	4	11.24
200 mg CSL312 SC single dose	157	433.38
200 mg CSL312 q4wk SC	166	3754.25
400 mg CSL312 q2wk SC	6	16.53
400 mg CSL312 q4wk SC	3	42.45
600 mg CSL312 SC single dose	4	11.01
600 mg CSL312 q4wk SC	24	270.88
75 mg CSL312 q4wk SC	9	26.68
Total (1)	**373**	**4670.75**
COVID-19 Indication		
Dose of Exposure	**Patients / Subjects**	**Person Time (months)**
700 mg CSL312 IV single dose	58	48.36
Total	**58**	**48.36**
IPF Indication		
Dose of Exposure (2)	**Patients / Subjects**	**Person Time (months)**
300 mg CSL312 IV single dose	35	11.43
600 mg CSL312 SC, week 2, 4, 10	31	116.80
Total (3)	**35**	**128.23**

CCI [redacted]

HAE = hereditary angioedema; IPF = idiopathic pulmonary fibrosis
(1) In counting number of subjects, each subject is counted only once.
(2) Due to the fact that CSL312_2002 study is ongoing and double-blinded, exposure summary results for CSL312 subjects are just estimated values based on the 1:1 randomisation ratio (CSL312 vs. Placebo) of the study.
(3) For this study, the 300 mg CSL312 IV is loading dose, therefore in calculating the total, each subject is counted only once.

Table SIII-4: Ethnic origin

Ethnic Origin	Patients / Subjects	Person-Time
Cumulative for All Indications		
Asian	71	619.43
Black	40	122.64
Caucasian	334	3980.32
Other	21	124.94
unknown	0	0
Total	**466**	**4847.34**
Ethnic Origin	**Patients / Subjects**	**Person Time**
HAE Indication		
Asian	69	617.99
Black	33	116.07
Caucasian	260	3823.15
Other	11	113.54
unknown	0	0
Total	**373**	**4670.75**
COVID-19 indication		
Asian	2	1.45
Black	6	4.67
Caucasian	41	35.12
Other	9	7.13
unknown	0	0
Total	**58**	**48.36**
Ethnic origin (1)	**Patients / Subjects**	**Person time**
IPF indication		

Ethnic Origin	Patients / Subjects	Person-Time
Asian	0	0
Black	1	1.91
Caucasian	33	122.05
Other	1	4.27
unknown	0	0
Total	**35**	**128.23**

HAE = hereditary angioedema; IPF = idiopathic pulmonary fibrosis
(1) Due to the fact that CSL312_2002 study is ongoing and double-blinded, exposure summary results for CSL312 subjects are just estimated values based on the 1:1 randomisation ratio (CSL312 vs. Placebo) of the study.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Concomitant diagnosis of another form of angioedema, such as idiopathic or acquired angioedema, recurrent angioedema associated with urticarial or HAE-nC1INH

Reason for exclusion in Phase 3 pivotal clinical study: To not interfere with the efficacy analyses of the study

Is it considered to be included as missing information? No

Rationale: Does not imply an additional risk for the subjects.

Note: Information on the prevalence of normal C1-esterase inhibitor HAE (HAE-nC1INH) is limited and generally characterised as unknown. In Phase 2 study for HAE (CSL312_2001), which was designed as a proof-of-concept and dose finding study, a total of 6 HAE-nC1INH patients were included to evaluate prophylactic treatment in this rare HAE patient subpopulation to generate clinical data. Overall, garadacimab was safe and well tolerated in all 6 HAE-nC1INH subjects enrolled in the Phase 2 study (CSL312_2001).

Any preplanned major surgeries or procedures during the clinical study

Reason for exclusion: Potential to trigger HAE attacks during the clinical study which may interfere with the efficacy analyses of the study.

Is it considered to be included as missing information? No

Rationale: Specific to the conduct of the clinical trial only

Use of C1INH products, androgens, antifibrinolytics or other small molecule medications for routine prophylaxis against HAE attacks

Reason for exclusion: To not interfere with the efficacy of the study.

Is it considered to be included as missing information? No

Rationale: Specific for accurate efficacy analysis.

Use of estrogen-containing medications with systemic absorption (eg, oral contraceptive or hormonal replacement therapy)

Reason for exclusion: To not interfere with the efficacy analyses of the study.

Is it considered to be included as missing information? No

Rationale: Does not imply an additional risk for the subjects.

Use of angiotensin-converting enzyme

Reason for exclusion: To not interfere with the efficacy or safety analyses of the study.

Is it considered to be included as missing information? No

Rationale: Does not imply an additional risk for the subjects.

Pregnant or breastfeeding or Intention to become pregnant or to father a child at any time during the study

Reason for exclusion: Common ethical practice to not include this patient subgroup at this stage of the clinical development program.

Is it considered to be included as missing information? Yes

Rationale: Not applicable

Known or suspected hypersensitivity to monoclonal antibody therapy or hypersensitivity to the investigational product or to any excipients of the investigational product.

Reason for exclusion: To not interfere with the safety analyses of the study.

Is it considered to be included as missing information? Yes

Rationale: Not applicable

The safety-relevant parameters of the above exclusion criteria are adequately addressed in the product labelling, and are either mentioned as absolute contraindications, relevant warnings / precautions, or as missing information.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency or those caused by prolonged / cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table SIV.3-1: Exposure of special populations included or not in clinical trial development programs

Type of Special Population	Exposure
Pregnant women Breastfeeding women	Females who are pregnant, breast feeding or planning a pregnancy during the study were excluded from the studies, and females who were of childbearing potential must have had a negative pregnancy test at screening. The exclusion of pregnant or lactating women (as well as women planning a pregnancy during a clinical study) is not product specific, but a general ethical requirement for most clinical trials. As of 16 June 2023, there were a total of 10 pregnancies reported from the clinical trials conducted on garadacimab (4 from 2001 study [2 female subjects and 2 male subject's female partner] and 6 pregnancies from 3002 study [1 female subject and 5 pregnancies in 4 male subject's female partner]).
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Populations with any co-morbidities that in the judgement of the investigator or the sponsor, may compromise their safety or compliance, impede successful conduct of the study, interfere with interpretation of the results, or would otherwise render the subject unsuitable for participation in the study are not included in the clinical development program.
Paediatric patients (Age < 12 years)	Garadacimab is currently being investigated by the SC route at a concentration of 100 mg/mL for the preventive treatment of HAE in pediatric subjects. The pediatric study is ongoing. No safety data are available as of the DLP of this RMP (CSL312_3003 study title: Phase 3 Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of Garadacimab in the Prophylactic Treatment of Hereditary Angioedema in Pediatric Subjects 2 to 11 Years of Age).
Population with relevant different ethnic origin	HAE affects all ethnic groups with no clear ethnic variation. Clinical studies as of the DLP of this RMP included Caucasian, Asian, Black, and subjects with ethnicity defined as "other".

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	<not included in the clinical development program>
Other	<not included in the clinical development program>

HAE = hereditary angioedema; DLP = data lock point; RMP = risk management plan; SC = subcutaneous

Part II: Module SV – Post-authorisation experience

Not applicable as garadacimab is not yet approved in any country.

SV.1 Post-authorisation exposure

Not applicable as garadacimab is not yet approved in any country.

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

Table SV.1.2-1: Exposure Table

Not applicable as garadacimab is not yet approved in any country.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Garadacimab is not known to have attributes that makes it a candidate for intentional overdose, abuse, or illegal use. Therefore, no potential for misuse for illegal purposes is anticipated.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The risks below were considered to have minimal clinical impact on patients (in relation to the severity of the indication treated), were expected due to the SC route of administration of garadacimab and were thus not considered important for inclusion in the list of safety concerns for the initial RMP:

Injection site reactions (injection site erythema, injection site pruritus, injection site pain, injection site bruising, injection site swelling, injection site urticaria etc).

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk:

There are no important risks which have been identified with garadacimab.

Important Potential Risk:

Severe hypersensitivity including anaphylaxis:

Risk-benefit impact:

Hypersensitivity and anaphylactic reactions have not been observed in the clinical trials conducted with garadacimab. Evidence from scientific literature supports a causal association and the risk is considered serious due to the potential life-threatening nature.

Based on supportive evidence from the scientific literature, severe hypersensitivity including anaphylaxis was considered to potentially impact the benefit-risk profile of garadacimab and

was therefore classified as important potential risk in the initial RMP (Cáceres et al, 2019; Sachs and Merk, 2018).

Routine pharmacovigilance and risk minimisation measures are implemented to help characterise the risk and ensure a positive benefit-risk balance for garadacimab during the clinical development program and after product launch as well.

Details about this potential risk is given in Section SVII.3.1.

Missing information:

The following are considered missing information with garadacimab.

1. Safety in pregnancy and breastfeeding
2. Long-term safety in adults
3. Long-term safety in adolescents

Details about the missing information are given in Section SVII.3.2.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as this is the first EU-RMP for garadacimab.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Potential Risk: Severe hypersensitivity including anaphylaxis

Potential Mechanisms:

Hypersensitivity reactions (HSRs) to mAbs include infusion-related reactions, cytokine-release reactions, type I (Immunoglobulin E / non-Immunoglobulin E), type III, and delayed type IV reactions. The difference between infusion-related reactions and

cytokine-release reactions is the self-limiting nature of infusion related reactions on repeat exposure and the response to premedication. Type I reactions are associated with the release of mast cells / basophils mediators, including tryptase, histamine, leukotrienes, and prostaglandins, whose actions affect cutaneous, respiratory, gastrointestinal, and cardiovascular organ systems leading to symptoms such as flushing, pruritus, urticaria, shortness of breath, hypotension, and life-threatening anaphylaxis. Type III HSRs arise when soluble antigens aggregate with Immunoglobulin G / Immunoglobulin M (immune complexes) that deposit in tissues and may cause injury either locally (Arthus reaction with mAb injection) or systemically. Delayed type IV HSRs may range from non-severe maculopapular rash to severe reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis. They typically arise from 12 hours to several weeks after exposure to the offending mAbs and are thought to be T-cell mediated but other mechanisms may be involved (Cáceres et al, 2019).

Evidence source(s) and strength of evidence:

Evidence source: Unconfirmed class effect as seen in literature (Cáceres et al, 2019; Sachs and Merk, 2018).

Evidence- Preclinical data: Immunological reactions are observed in repeat-dose toxicological studies which are considered not predictive for the clinical situation, in line with the ICH S6(R1) guideline (ICH S6(R1), 1997) as they are principally expected after repeat dosing of heterologous proteins (ie, human proteins in animal species).

Characterisation of the risk:

Frequency (estimated): Clinical data: Severe hypersensitivity including anaphylaxis was not reported in completed (1001, 1003, 1004, 2001, 3001) and ongoing studies (3002 and 3003) conducted on garadacimab as of 16 June 2023.

Severity and Nature of Risk: Identification of drug induced hypersensitivity reaction is challenging given the myriad of symptoms and clinical presentations associated with the condition. Anaphylaxis generally involves an acute onset (minutes to several hours), and can involve the skin, mucosal tissue and/or gut symptoms, with respiratory compromise and / or reduced blood pressure. Anaphylaxis can be life-threatening; however, most reactions do not result in severe outcomes, with the case fatality rate estimated at 0.001% (Anagnostou and Turner, 2019).

Background incidence / Prevalence: In the HAE populations, the background incidence of hypersensitivity / anaphylactic reactions is not known. In the general population, it is estimated that 10 to 20% of adults suffer from at least 1 allergic disease (Behrendt and Ring, 2012). Non-food-related anaphylaxis occurred predominantly in adults over the age of 35 years (Poulos et al, 2007).

Risk factors and risk groups:

Throughout the evolution from murine, chimeric, and humanised to completely human products, there has been a significant reduction in the immunogenic risks associated with mAbs that resemble endogenous human immunoglobulins more closely (Cui et al, 2017). As garadacimab is a fully human IgG4 mAb, the risk of HSRs is expected to be minimal. However, an inherent risk of developing a HSR to any product should be considered when giving a product for the first time.

In case of the different kinds of HSRs, the non-allergic acute HSRs (also known as anaphylactoid or a non-Immunoglobulin E–mediated reaction) usually already occur with the first application and their symptoms decrease with subsequent use. Real allergic reactions (immunoglobulin (Ig) E-mediated) usually do not manifest themselves when used for the first time, as a sensitisation phase must precede them. However, if preformed or cross-reacting antibodies are present in the patient, the allergic reactions can also occur with the first application (Sachs and Merk, 2018).

Pre-medications such as acetaminophen, anti-histaminic or corticosteroids are considered as standard procedure for keeping the risk for HSRs with mAbs to a minimum. However, due to the fact that most injection reactions with mAbs take place following the first or second infusion, the value of premedication on subsequent infusions may decrease (Cáceres et al, 2019).

Preventability:

Garadacimab is contraindicated in HAE patients with a history of hypersensitivity to the active substance or to any of the excipients of garadacimab, which is stated in the label.

Additionally, the warnings and precautions section states that HSRs, although not observed in garadacimab's clinical trials, may theoretically occur. The label further advised that in case of severe hypersensitivity, patients should discontinue garadacimab administration and institute appropriate treatment.

CCI [redacted]

Impact on the risk-benefit balance of the product:

Severe hypersensitivity including anaphylaxis is an important potential risk with garadacimab which is included when determining the benefit-risk balance of garadacimab. Routine pharmacovigilance activities have been implemented including, but not limited to ongoing signal detection, literature review and aggregate reporting and using a specific follow up questionnaire to gather detailed information specific to the HSRs including anaphylaxis. These routine pharmacovigilance activities in addition to inclusion of the risk in the label under contraindications and warnings and precautions for use ensures a favourable benefit-risk balance for garadacimab.

Public health impact:

No public health impact is anticipated due to standard health care practices.

SVII.3.2 Presentation of the missing information

Missing information 1: Safety in pregnancy and breastfeeding

Evidence source: There is limited clinical study data on the effects of garadacimab in pregnant and lactating women. The label recommends avoiding its use during pregnancy and during breast feeding. Hence, the risk to be anticipated with garadacimab when used in pregnant and lactating women is yet to be characterised.

In nonclinical studies, an animal reproductive toxicity study in rabbits found no treatment-related toxicologically relevant effects on embryo-fetal survival and development, when garadacimab is administered during the organogenesis stage of pregnancy.

As of 16 June 2023, there are 10 pregnancies reported from the clinical trials conducted on garadacimab (4 from 2001 study [2 female subjects and 2 female partners of male subjects] and 6 from 3002 study [1 female subject and 5 pregnancies in 4 male subject's female partner]). Of these 10 pregnancies, the pregnancy outcome was reported to be normal with no maternal complications during labour or any birth defect, congenital abnormalities, or perinatal complications to the babies in 6 cases and not available in 2 cases where no further information was received yet. In 1 case (female partner of male subject), the pregnancy outcome was reported as spontaneous abortion (less than 22 weeks), but no Follow-up information could be obtained. In 1 case, the pregnancy is ongoing. No safety findings associated with garadacimab were reported from these pregnancies.

Routine pharmacovigilance measures including, but not limited to ongoing signal detection, literature review and aggregate reporting are implemented to gather information on any pregnancies reported from post-marketing experience.

Missing information 2: Long-term safety in adults

Evidence source: There is limited clinical study data on the long-term safety of garadacimab in adults. Hence, the safety profile of CSL312 for long-term use in adults needs to be characterized further.

The Phase 3 (VANGUARD) open-label extension study (CSL312_3002) is evaluating long-term safety and efficacy of CSL312 in adults with HAE. As of 16 June 2023, there are 138 adult subjects who had an exposure of more than 12 months, 74 adult subjects with more than 18 months of exposure and 31 more than 21 months of exposure. No safety findings or differences in the safety profile of CSL312 have been identified for adults during the time of the open-label extension study.

CSL312 is indicated for the chronic treatment of patients, and therefore, it is important to sufficiently characterize its long-term safety profile.

Missing information 3: Long-term safety in adolescents

Evidence source: There is limited clinical study data on the long-term safety of garadacimab in adolescents. Hence, the safety profile of CSL312 for long-term use in adolescents, needs to be characterized further.

The Phase 3 (VANGUARD) open-label extension study (CSL312_3002) is evaluating long-term safety and efficacy of CSL312 in adolescents with HAE. As of 16 June 2023, 90% of the adolescent subjects (9 of 10) had an exposure of more than 12 months and 2 adolescents with more than 18 months of exposure. No safety findings or differences in the safety profile of CSL312 have been identified for adolescents during the time of the open-label extension study.

CSL312 is indicated for the chronic treatment of patients, including treatment of adolescents and therefore, it is important to sufficiently characterize its long-term safety profile.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII-1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Severe hypersensitivity including anaphylaxis
Missing information	• Safety in pregnancy and breastfeeding • Long-term safety in adults • Long-term safety in adolescents

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the potential risk of severe hypersensitivity including anaphylaxis:

Follow-up questionnaire on Allergic / Anaphylactic Reactions. Please see Annex 4 for details on this questionnaire.

Please see Annex 4 for details on this questionnaire.

III.2 Additional pharmacovigilance activities

All safety information will continue to be monitored in accordance with Good Pharmacovigilance Practice including regular review and evaluation of data.

Study short name and title:

Garadacimab Non-Interventional Post-Authorisation Safety Study: Long Term Safety in Adults and Adolescents

Rationale and study objectives:

CSL Behring will conduct a non-interventional Post-Authorisation Safety Study with garadacimab in adults and adolescents with HAE in an observational manner in a real-world setting to further characterize the missing information of Long-term safety in adults and Long-term safety in adolescents.

Primary Objective: To describe the real-world long-term safety profile of garadacimab in adult and adolescent participants with HAE.

Exposure: Exposure to garadacimab for HAE long-term prophylaxis over a targeted follow-up period of 4 years according to routine clinical practice and physician discretion.

Endpoints:

1. Incidence rate and characteristics of AEs while on treatment with garadacimab (eg, AE term, severity, seriousness, duration, relatedness and event outcome) in adults and adolescents.
2. In adolescents, impact of garadacimab on sexual maturation, bone growth and cognitive development. This study will employ assessments to measure these outcomes, such as Tanner staging to assess sexual maturation, standardized growth charts for bone growth, and academic performance for cognitive development.

Study Design:

This will be a non-interventional, observational cohort study conducted with a targeted follow-up period of 4 years.

Study Population:

The study will include approximately 150 individuals with HAE ≥12 years of age and who have been prescribed garadacimab by their treating physician for treatment of HAE.

Milestones:

Submission of feasibility assessment in April 2025 (within 3 months of EC decision).

Protocol submission in April 2025 (within 3 months of EC decision).

Registration in the EU PAS Register in February 2026. Study start in April 2026.

Study completion in April 2034.

Final study report in April 2035.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.3-1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Garadacimab Non-Interventional Post-Authorisation Safety Study: Long Term Safety in Adults and Adolescents Planned	Primary Objective: To describe the real-world long-term safety profile of garadacimab in adult and adolescent participants with HAE. Endpoints: 1. Incidence rate and characteristics of AEs while on treatment with garadacimab (eg, AE term, severity, seriousness, duration, relatedness and event outcome) in adults and adolescents. 2. In adolescents, impact of garadacimab on sexual maturation, bone growth and cognitive development. This study will employ assessments to measure these outcomes, such as Tanner staging to assess sexual maturation, standardized growth charts for bone growth, and academic performance for cognitive development.	Long-term safety in adults and Long-term safety in adolescents	Submission of feasibility assessment	April 2025 (within 3 months of EC decision)
			Protocol submission to EMA	April 2025 (within 3 months of EC decision)
			Registration in the EU PAS Register	February 2026
			Start of study	April 2026
			Study completion	April 2034
			Final report of study results	April 2035

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	Study Design and Participants: This will be a non-interventional, observational cohort study conducted with a targeted follow-up period of 4 years. The study will include approximately 150 individuals with HAE ≥12 years of age and who have been prescribed garadacimab by their treating physician for treatment of HAE.			

Part IV: Plans for post-authorisation efficacy studies

There are currently no plans or specific obligations for any post-authorisation efficacy studies for garadacimab for the HAE indication.

Table Part IV-1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine risk minimisation measures

Table Part V.1-1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important potential risk	
Severe hypersensitivity including anaphylaxis	Routine risk communication: SmPC Section 4.3 (Contraindications), 4.4 (Warnings and precautions for use) Patient Information Leaflet Section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product
Missing information	
Safety in pregnancy and breastfeeding	Routine risk communication: SmPC Section 4.6 (Fertility, pregnancy and lactation) Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product
Long-term safety in adults	Routine risk communication: SmPC Section 4.2 (Posology and method of administration), 4.4 Special warnings and precautions for use Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product
Long-term safety in adolescents	Routine risk communication: SmPC Section 4.8 (Paediatric population), 5.1 Pharmacodynamic properties Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product

SmPC = summary of product characteristics

V.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe hypersensitivity including anaphylaxis	Routine risk communication: SmPC Section 4.3 (Contraindications), 4.4 (Warnings and precautions for use) PL Section 4 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire on Allergic / Anaphylactic Reactions Additional pharmacovigilance activities: None
Safety in pregnancy and breastfeeding	Routine risk communication: SmPC Section 4.6 (Fertility, pregnancy, and lactation) Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in adults	Routine risk communication: SmPC Section 4.2 (Posology and method of administration), 4.4 Special warnings and precautions for use Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Post-Authorisation Safety Study to further characterise long-term safety in adults.
Long-term safety in adolescents	Routine risk communication: SmPC Section 4.8 (Paediatric	Routine pharmacovigilance activities beyond adverse reactions reporting and

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	population), 5.1 Pharmacodynamic properties Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only product Additional risk minimisation measures: None	signal detection: None Additional pharmacovigilance activities: Post-Authorisation Safety Study to further characterise long-term safety in adolescent patients.

PL = patient leaflet; SmPC = summary of product characteristics

Part VI: Summary of the risk management plan

Summary of risk management plan for garadacimab

This is a summary of the RMP for garadacimab. The RMP details important risks of garadacimab, how these risks can be minimised, and how more information will be obtained about garadacimab's risks and uncertainties (missing information).

Garadacimab's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how garadacimab should be used.

This summary of the RMP for garadacimab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of garadacimab's RMP.

I. The medicine and what it is used for

Garadacimab is investigated for routine prevention of recurrent attacks of HAE in patients aged 12 years and older (see SmPC for the full indication). Garadacimab is a factor XIIa inhibitor monoclonal antibody as the active substance, and it is given subcutaneously.

Further information about the evaluation of garadacimab's benefits can be found in garadacimab's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage link to the EPAR summary landing page.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of garadacimab, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size - the amount of medicine in a pack is chosen to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures. In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of garadacimab is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of garadacimab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential, with only important potential risks identified for garadacimab to date. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Severe hypersensitivity including anaphylaxis
Missing information	• Safety in pregnancy and breastfeeding • Long-term safety in adults • Long-term safety in adolescents

II.B Summary of important risks

Important potential risk: Severe hypersensitivity including anaphylaxis	
Evidence for linking the risk to the medicine	Evidence source: Unconfirmed class effect as seen in literature (Cáceres et al, 2019; Sachs and Merk, 2018).
Risk factors and risk groups	Throughout the evolution from murine, chimeric, and humanised to completely human products, there has been a significant reduction in the immunogenic risks associated with mAbs that resemble endogenous human immunoglobulins more closely (Cui et al, 2017). As garadacimab is a fully human IgG4 mAb, the risk of HSRs is expected to be minimal. However, an inherent risk of developing a HSR to any product should be considered when giving a product for the first time. In case of the different kinds of HSRs, the non-allergic acute HSRs (also known as anaphylactoid or a non-Immunoglobulin E–mediated reaction) usually already occur with the first application and their symptoms decrease with subsequent use. Real allergic reactions (immunoglobulin (Ig) E-mediated) usually do not manifest themselves when used for the first time, as a sensitisation phase must precede them. However, if preformed or cross-reacting antibodies are present in the patient, the allergic reactions can also occur with the first application (Sachs and Merk, 2018). Pre-medications such as acetaminophen, anti-histaminic or corticosteroids are considered as standard procedure for keeping the risk for HSRs with mAbs to a minimum. However, due to the fact that most injection reactions with mAbs take place following the first or second infusion, the value of premedication on subsequent infusions may decrease (Cáceres et al, 2019).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 (Contraindications), 4.4 (Warnings and precautions for use) PL Section 4 Additional risk minimisation measures: None
Missing Information: Safety in pregnancy and breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 (Fertility, pregnancy, and lactation) Additional risk minimisation measures: None
Missing Information: Long-term safety in adults	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, 4.4 Additional risk minimisation measures:

CCI [redacted]

	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-Authorisation Safety Study to further characterise Long-term safety in adults and Long-term safety in adolescent patients. See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Long-term safety in adolescents	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 (Paediatric population), 5.1 Pharmacodynamic properties Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-Authorisation Safety Study to further characterise Long-term safety in adults and Long-term safety in adolescent patients. See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of garadacimab.

II.C.2 Other studies in post-authorisation development plan

The following additional pharmacovigilance activities are included in the post-authorisation development plan:
Category 3: Garadacimab Non-Interventional Post-Authorisation Safety Study: Long Term Safety in Adults and Adolescents

Purpose of the planned study:

CSL Behring will conduct a non-interventional Post-Authorisation Safety Study with garadacimab in adults and adolescents with HAE in an observational manner in a real-world

setting to further characterize the missing information of Long-term safety in adults and Long-term safety in adolescents.

Primary Objective: To describe the real-world long-term safety profile of garadacimab in adult and adolescent participants with HAE.

Exposure: Exposure to garadacimab for HAE long-term prophylaxis over a targeted follow-up period of 4 years according to routine clinical practice and physician discretion.

Endpoints:

1. Incidence rate and characteristics of AEs while on treatment with garadacimab (eg, AE term, severity, seriousness, duration, relatedness and event outcome) in adults and adolescents.
2. In adolescents, impact of garadacimab on sexual maturation, bone growth and cognitive development. This study will employ assessments to measure these outcomes, such as Tanner staging to assess sexual maturation, standardized growth charts for bone growth, and academic performance for cognitive development.

Study Design:

This will be a non-interventional, observational cohort study conducted with a targeted follow-up period of 4 years.

Study Population:

The study will include approximately 150 individuals with HAE ≥12 years of age and who have been prescribed garadacimab by their treating physician for treatment of HAE.

Milestones:

Submission of feasibility assessment in April 2025 (within 3 months of EC decision).

Protocol submission in April 2025 (within 3 months of EC decision).

Registration in the EU PAS Register in February 2026.

Study start in April 2026.

Study completion in April 2034.

Final study report in April 2035.

Garadacimab Non-Interventional Post-	Primary Objective: To describe the real-world long-term safety profile of garadacimab in adult and adolescent participants with HAE.	Long-term safety in adults and Long-term	Submission of feasibility assessment	April 2025 (within 3 months of EC decision)

Authorisation Safety Study: Long Term Safety in Adults and Adolescents Planned	Endpoints: 1. Incidence rate and characteristics of AEs while on treatment with garadacimab (eg, AE term, severity, seriousness, duration, relatedness and event outcome) in adults and adolescents. 2. In adolescents, impact of garadacimab on sexual maturation, bone growth and cognitive development. This study will employ assessments to measure these outcomes, such as Tanner staging to assess sexual maturation, standardized growth charts for bone growth, and academic performance for cognitive development. Study Design and Participants: This will be a non-interventional, observational cohort study conducted with a targeted follow-up period of 4 years. The study will include approximately 150 individuals with HAE ≥12 years of age and who have been prescribed garadacimab by their treating physician for treatment of HAE.	safety in adolescents	Protocol submission	April 2025 (within 3 months of EC decision)
			Registration in the EU PAS Register	February 2026
			Start of study	April 2026
			Study completion	April 2034
			Final report of study results	April 2035

Part VII: Annexes

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Annex 4 Specific adverse drug reaction follow-up forms

Table of contents

Annex 4.1 Questionnaire on Allergic / Anaphylactic Reactions

Questionnaire on Allergic / Anaphylactic Reactions for all Products

CSL EMPLOYEE/AFFILIATE USE ONLY

Global CSL Reference Number _____
Local tracking number: _____

Date of awareness of report (dd/mmm/yyyy): _____ ☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	Date of Birth (DD/MMM/YYYY)	Age (at event onset) years Or Age Group	Gender ☐ Male ☐ Female ☐	Weight (at event onset) ☐ kg ☐ lb	Height (at event onset) ☐ cm ☐ in	Race (where local law allows) ☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify):

2. Patient History

Does the patient have any previous history of allergic reactions or hypersensitivity to:

Animal Hair?	Yes ☐	No ☐
Bee venom or wasp venom?	Yes ☐	No ☐
Food?	Yes ☐	No ☐
Grass and tree pollen?	Yes ☐	No ☐
Medication?	Yes ☐	No ☐
Others?	Yes ☐	No ☐

If 'yes' for any of the above, specify:

Does the patient have any previous history of:

Atopic dermatitis?	Yes ☐	No ☐
Extrinsic asthma?	Yes ☐	No ☐
Allergic rhinitis?	Yes ☐	No ☐
Others?	Yes ☐	No ☐

If 'yes' for any of the above, specify:

Does the patient have a family history of allergic predisposition (atopic disorders, etc.)? Yes ☐ No ☐

If 'yes', specify:

What is the patient's occupation? :

Concomitant / Confounding Factors:

Alcohol?	Yes ☐	No ☐
Infections?	Yes ☐	No ☐
Medication?	Yes ☐	No ☐
Menstruation?	Yes ☐	No ☐
Physical strain?	Yes ☐	No ☐
Stress?	Yes ☐	No ☐

If 'yes' for any of the above, specify:

CSL Behring Innovation GmbH * Global Clinical Safety & Pharmacovigilance * P O Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 * CSL Behring LLC * Global Clinical Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U S A * Fax +1-610-878-4487 * CSL * Global Clinical Safety & Pharmacovigilance * 45 Poplar Road * Parkville, Victoria Australia 3052 * Fax +61-3-9389-1095 *

Email: Adverse Events Global@cslbehring com

Questionnaire on Allergic / Anaphylactic Reactions for all Products

3. Previous Exposure to Medicinal Products

Has the patient previously been treated with either the same CSL product or other products containing the same active ingredient? Yes ☐ No ☐ Unknown ☐

If 'yes':

- Provide the therapy dates / total exposure. Specify the name of the product as well as the batch number along with the dates*:
- Were previous product administrations / applications tolerated? Yes ☐ ☐ No If 'no', describe symptoms and therapeutic measures:

4. Medicinal Product Exposure

Provide all therapy dates with CSL product(s) prior to onset of the symptoms of allergic / anaphylactic reaction, including batch numbers and exact dosage of each single administration:

Product(s):	Batch no and exact dosage(s):	Exact therapy dates (dd/mmm/yyyy):

Time interval between administration and onset of the allergic / anaphylactic reaction (specify in minutes, hours etc):

5. Information on the allergic / anaphylactic reaction - Did patient exhibit any of the following symptoms:

Skin:			Circulatory System:		
- Flush	Yes ☐	No ☐	- Chills, rigors	Yes ☐	No ☐
- Pruritus (itching)	Yes ☐	No ☐	- Circulatory arrest	Yes ☐	No ☐
- Rash	Yes ☐	No ☐	- Dizziness	Yes ☐	No ☐
- Swelling of face / angioedema	Yes ☐	No ☐	- Fainting or syncope	Yes ☐	No ☐
- Urticaria	Yes ☐	No ☐	- Hypotension	Yes ☐	No ☐
- Other?, specify:			- Vertigo	Yes ☐	No ☐
			- Other?, specify:		
Gastrointestinal System:			**Mucosa:**		
- Abdominal cramps	Yes ☐	No ☐	- Prickling or tingling of mouth	Yes ☐	No ☐
- Abdominal pain	Yes ☐	No ☐	- Swelling of lips, tongue or throat	Yes ☐	No ☐
- Diarrhea	Yes ☐	No ☐	- Other?, specify:		
- Nausea	Yes ☐	No ☐			
- Vomiting	Yes ☐	No ☐			
- Other?, specify:					

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Email: Adverse Events Global@cslbehring com

CSL	Questionnaire on Allergic / Anaphylactic Reactions for all Products

Respiratory System:		
- Cough	Yes ☐	No ☐
- Respiratory arrest	Yes ☐	No ☐
- Shortness of breath	Yes ☐	No ☐
- Wheezing	Yes ☐	No ☐
- Other?, specify:		
Were symptoms considered to be part of an anaphylactic reaction:	Yes ☐	No ☐
If applicable, provide any alternative diagnosis:		

6. Laboratory confirmation of allergic / anaphylactic reaction (including measurements of vital signs) if applicable:

Measurement	Result	Units/Normal range if applicable	Date and Time
Temperature			
Blood Pressure			
Heart Rate			
Respiratory Rate			
Total IgE			
Specific RAST (Radioallergosorbent test)			
Skin Prick Test			
Serum Mast Cell Tryptase			
Other:			

7. Concomitant medications? (exclude those used to treat reaction) Yes ☐ If yes, specify below No ☐ Unknown ☐

Drug	Dose	Route	Indication for Use	Start date	Stop date

CSL Behring Innovation GmbH * Global Clinical Safety & Pharmacovigilance * P O Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 * CSL Behring LLC * Global Clinical Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U S A * Fax +1-610-878-4487 * CSL * Global Clinical Safety & Pharmacovigilance * 45 Poplar Road * Parkville, Victoria Australia 3052 * Fax +61-3-9389-1095 *

Email: Adverse Events Global@cslbehring com

Questionnaire on Allergic / Anaphylactic Reactions for all Products

8. Treatment and Outcome

Describe therapeutic measures (e.g. antihistamines, steroids, epinephrine, ß2-agonists, including route of administration (IV, IM, inhaler); venous access; hospitalisation etc.):

Outcome:

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ *provide sequelae*
Recovered with treatment ☐ *provide details*

If patient recovered, provide date recovered:

9. Further Medication of the Patient

Will the patient continue with CSL products?	Yes ☐	No ☐
Will the patient be premedicated prior to further administrations?	Yes ☐	No ☐
If 'yes', specify		

☐ **No Further Information Available**

10. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see https //www.cslbehring.com/contact/report-an-undesirable-effect for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter	**Details of Treating Health Care Professional** (If different from Reporter)
Is this a consumer / patient report? ☐ Yes ☐ No	
(If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ yes ☐ No	
If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable