CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

garadacimab (TBC)

(CSL Behring Canada Inc)

Indication: For routine prevention of attacks of hereditary angioedema (HAE) in adult and pediatric patients (aged 12 years and older).

August 2, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Input Template for CDA Reimbursement Reviews

Name of Drug: garadacimab
Indication: Hereditary Angioedema (HAE)
Name of Patient Group: HAE Canada
Author of Submission: HAEC Advocacy Committee and Board of Directors

1. About Your Patient Group

HAE Canada (www.haecanada.org) is dedicated to creating awareness about HAE and other related angioedema, to helping expedite the diagnosis of patients and enabling patients to become champions for their own quality of life. We equip patients, caregivers, family members and health care providers with the information, tools and resources they need to ensure that those with HAE and other related angioedema can live healthy and productive lives. Additionally, HAE Canada is committed to improving patient access to Health Canada approved treatments for hereditary angioedema and other related angioedema.

2. Information Gathering

In July 2024, HAE Canada (HAEC) developed a patient survey specifically for patients with experience with Garadacimab (CSL312), a novel, fully human monoclonal antibody that inhibits activated factor XII (FXIIa) - a different mode of action from any other approved treatment. HAEC contacted Canadian physician investigators who had patients enrolled in the Vanguard Study and requested that they provide these patients with the survey so that we could obtain their insights regarding their challenges with hereditary angioedema and their experiences with garadacimab. Fourteen (n=14) patients responded to this survey.

Patients who responded to this survey were also asked if they would be willing to participate in telephone interviews to better understand their experiences with garadacimab, their experiences with other HAE treatments, and the challenges they experience living with HAE.

Also, in June and July 2024, HAE Canada conducted our 3rd National Survey to inform our National Report Card. This survey was designed for patients and caregivers to better understand the needs and experiences of patients with HAE and to inform HAE Canada's policy and advocacy activities related to improving access to safe and effective treatments.

The themes that emerged in this research highlight the challenges and desires related to the management of Hereditary Angioedema (HAE), including the need for better treatment options, financial concerns, and the impact on daily life. The data emphasizes the transformative impact of garadacimab on patients with HAE, highlighting its effectiveness, ease of use, and the significant improvement in the quality of life for those affected.

3. Disease Experience

Hereditary angioedema (HAE) is a severely debilitating and life-threatening disease. It manifests as unpredictable, recurrent/intermittent edema attacks in different parts of the body including the gastrointestinal tract, upper respiratory tract, extremities and face. Gastrointestinal (GI) attacks are common in HAE, with severe abdominal pain and other GI symptoms. Untreated laryngeal attacks may result in asphyxiation and death. Swelling in other body parts can also significantly interfere with patients' daily pursuits, resulting in a severely impaired quality of life.

In our 2024 National Survey we asked: ***Please rate how HAE impacts you according to the following factors:****.1 is "no impact" and 6 is "very high impact".* We had 13 categories as follows (see data visualization chart on following page):

	NO IMPACT	VERY LOW IMPACT	LOW IMPACT	MODERATE IMPACT	HIGH IMPACT	VERY HIGH IMPACT	N/A	TOTAL	WEIGHTED AVERAGE
Social and personal well-being	13.85% 9	10.77% 7	13.85% 9	30.77% 20	10.77% 7	15.38% 10	4.62% 3	65	2.89
Ability to pursue advanced education	18.46% 12	9.23% 6	7.69% 5	12.31% 8	7.69% 5	12.31% 8	32.31% 21	65	2.68
Ability to attend school regularly	20.00% 13	4.62% 3	7.69% 5	6.15% 4	1.54% 1	12.31% 8	47.69% 31	65	2.50
Ability to work a full-time job	16.92% 11	7.69% 5	16.92% 11	7.69% 5	7.69% 5	18.46% 12	24.62% 16	65	2.82
Ability to have healthy relationships with friends and family	30.77% 20	10.77% 7	15.38% 10	24.62% 16	6.15% 4	4.62% 3	7.69% 5	65	2.22
Ability to participate in physical activities	16.92% 11	15.38% 10	15.38% 10	20.00% 13	13.85% 9	12.31% 8	6.15% 4	65	2.72
Ability to have a healthy lifestyle	24.62% 16	18.46% 12	15.38% 10	13.85% 9	12.31% 8	9.23% 6	6.15% 4	65	2.44
Career advancement	25.00% 16	6.25% 4	14.06% 9	4.69% 3	4.69% 3	14.06% 9	31.25% 20	64	2.45
Financial well-being	24.62% 16	7.69% 5	18.46% 12	9.23% 6	12.31% 8	15.38% 10	12.31% 8	65	2.63
Ability to effectively parent	18.46% 12	6.15% 4	6.15% 4	10.77% 7	4.62% 3	6.15% 4	47.69% 31	65	2.38
Ability to retire as planned	18.46% 12	9.23% 6	9.23% 6	6.15% 4	6.15% 4	16.92% 11	33.85% 22	65	2.77
Fear of having an attack while traveling	9.23% 6	3.08% 2	12.31% 8	27.69% 18	16.92% 11	26.15% 17	4.62% 3	65	3.37
Concerns about having children due to hereditary nature of disease	10.77% 7	4.62% 3	6.15% 4	6.15% 4	7.69% 5	18.46% 12	46.15% 30	65	3.23

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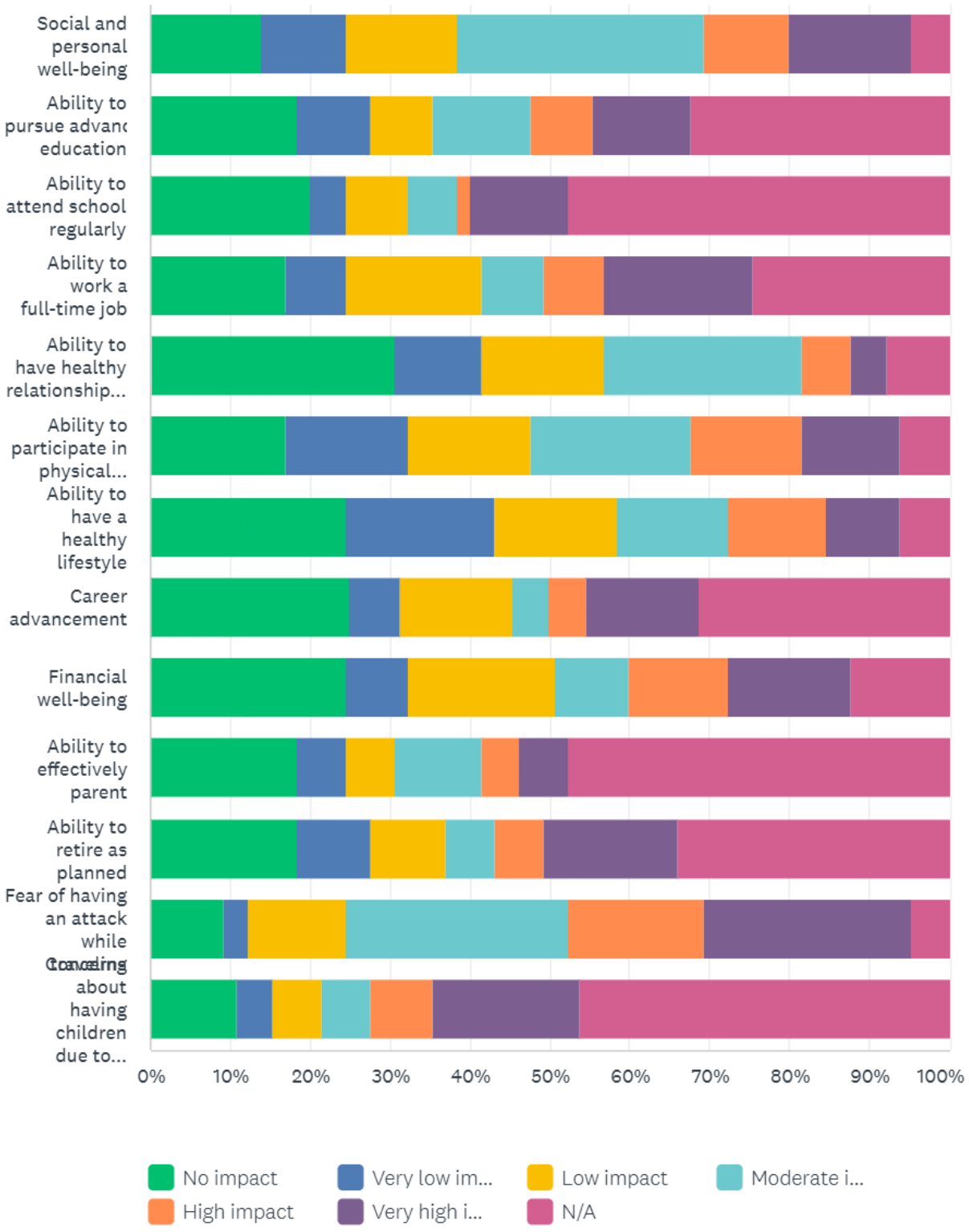
HAE impacts: Data Visualization



In our 2024 National Survey we also asked: Living with HAE, ***which of the following factors are you most worried about? Please select all that apply.***

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ANSWER CHOICES		RESPONSES	
Regular fear of experiencing unpredictable and debilitating attacks		61.54%	40
The pain associated with the attacks		52.31%	34
Passing the disease to children		52.31%	34
Experiencing airway/laryngeal attack		75.38%	49
Social isolation and/or stigmatization		18.46%	12
Experiencing an attack in a social setting		35.38%	23
HAE interfering in a relationship		27.69%	18
Birth control pills containing estrogen potentially triggering an HAE attack		13.85%	9
HAE compromising a safe pregnancy		12.31%	8
Genital swelling		13.85%	9
Alcohol consumption potentially triggering an HAE attack		18.46%	12
Not applicable		4.62%	3
Other (please specify). Please share any other comments you have below.	Responses	21.54%	14
Total Respondents: 65			

Respondents were also given an opportunity to share other comments/explain further. The themes of these comments included the following: restriction of activities, fatigue, guilt, symptom control, age-related issues, impact on sleep and employment, satisfaction with treatment, symptom management, and needle phobia

Here are comments in their own words:

-Restriction on activities especially in summer months.
2024-07-17 09:13 p.m.

-Fatigue
2024-07-01 09:07 p.m.

-Guilt. I gave HAE to all 3 of our kids. We've missed out on so much of life and their childhood activities because I was too sick.
2024-06-30 11:31 p.m.

-Now that my symptoms are controlled and I never have attacks the things that used to worry me do not any more. Before finding meds that stop my attacks I would fill in most of the list above.
2024-06-27 11:46 a.m.

-I experienced some of the above when I was young but at my current age 72 none of these things are an issue anymore.
2024-06-26 04:18 p.m.

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-not getting enough sleep, doing to much at work, stigma of "being sick", feeling like it is something I did to cause attack, wishing I could afford easier treatment
2024-06-26 12:40 p.m.

-Happy with my present treatment- works great!
2024-06-26 12:14 a.m.

-Having an attack and not making it to the washroom. Being incontinent of stool. Especially when being active away from the house. Constant worry about knowing if there is a bathroom close. Because an attack could just happen.
2024-06-25 11:46 p.m.

-Not worried about anything. I have the disease, get the attacks and use the treatment.
2024-06-25 10:41 p.m.

-Fear and pain of needles. Sense of utter panic washing over with attack onset.
2024-06-18 09:11 p.m.

-Causing stress to a few people left in my life
2024-06-17 07:35 p.m.

-I have laryngeal, and chest swells. My throat is never fully open. Scared they would not be able to intubate me. Tracheotomy might be too late. Scared of choking to death or heart swell is really a heart attack!
2024-06-13 08:01 p.m.

-Inability to retire abroad because of lack of treatment options
2024-06-12 09:34 p.m.

-The interplay of aging with HAE. I wonder what would happen if/when I am depending on others to administer C1 if I should be unable to do it myself when I first feel it coming on. I wonder about the interplay of "aging" medications affecting HAE and triggering swellings. Like if I have heart disease or a heart attack, how would those medications affect my HAE, and would caretakers know what they are seeing to treat internal swellings before they were life threatening to me.
2024-06-12 06:00 p.m.

Conclusion:
Patients may still be affected by HAE even after the physical symptoms of an attack abate. For many, the anticipation or fear of HAE attacks imposes extreme or unacceptable limits on activities and plans. Due to the unpredictable nature of the disease, many patients experience high levels of distress and anxiety in everyday life, often attributed to restricted or disrupted social life, anxiety due to fear of future attacks, the fear of HAE being passed to their children, and disruption/interference in educational and career pursuits. A significant number of patients report that they do not pursue higher education due to HAE, and that they deliberately elect to not seek out certain jobs, and job advancements, due to expected recurrent edema attacks.

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4. Experiences With Currently Available Treatments

Areas of Unmet Need

Recognizing the burden to patients associated with HAE, including the ever-present risk of experiencing a life-threatening laryngeal attack, improved preventative treatments are urgently needed. Patients that may have the greatest unmet need for an intervention such as subcutaneously administered, once monthly garadacimab are:

i) Patients who find current prophylactic treatments to be ineffective

There is no current way to predict who will respond best to any current treatment for HAE, and while some patients respond extremely well to certain treatments, others do not. This heterogeneity in response to treatment drives an urgent need for treatment options for Long-term Prophylaxis (LTP). This variability is seen even with siblings and within families. One person may respond well to a treatment and another not at all.

Note: The mode of action of garadacimab is completely different than any other approved treatment, directly inhibiting activated factor XII (FXIIa), which makes it an important alternative choice of therapy.

ii) Patients who experience damage to their veins, or worry about future damage to their veins

Many patients who use intravenous treatment for prolonged periods experience extensive damage to their veins at the injection site(s). These patients urgently require treatment with another method of administration and/or less frequent administration. Subcutaneously administered treatments offer an important option for these patients.

iii) Patients who find it difficult and uncomfortable to self-administer intravenous treatments for HAE

Many patients have reported that they have difficulty self-administering intravenous treatment for HAE. This can be a function of a patient having damaged veins, or having difficulty finding a vein for intravenous infusion, or simply having great discomfort or general difficulty with the self-administration of an IV treatment (especially during an HAE attack).

iv) Patients who live far away from hospital care

IV HAE treatments have the effect of requiring patients to spend much time traveling to treatment and undergoing treatment; especially if they have difficulty doing home infusions. Patients who live in rural areas are particularly vulnerable.

v) Patients concerned about risk of infectious agent transmission and supply interruptions / shortages from plasma-derived HAE treatments

Even though multiple critical steps are taken to minimize the risk of infection from transfusion of blood products, the risk of infectious agent transmission from plasma-derived products, in some cases, drives patient preference for non-plasma derived treatments.

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vi) Patients with HAEn-C1-INH

There are currently no approved treatments for HAEn-C1-INH in Canada. The only therapy currently available for this type of HAE is plasma derived C1 inhibitor. Six types of HAE-nC1-INH are currently recognized, based on underlying mutations of:

1. factor XII (FXII),
2. angiopoietin-1 (ANGPT1)
3. plasminogen (PLG)
4. kininogen 1 (KNG1)
5. myoferlin (MYOF)
6. heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6).

However, in many patients with HAE-nC1-INH, no gene mutation has been found (HAE-UNK), but whole genome sequencing is still in early phases.

vii) Demand for Plasma

Of importance, Canadian Blood Services (CBS) recognizes that the use and demand for plasma-derived therapies continue to rise globally, while the percentage of plasma-derived products produced from plasma collected at Canadian donor centers is decreasing. While CBS is working to develop capacity to collect more plasma domestically to address plasma supply issues, an important strategy to lessen demand for these therapies is to offer patients *non-plasma* derived therapies when such therapies offer the required efficacy, safety and convenience for patients.

2024 National Survey

In our 2024 National Survey, we asked patients to ***Please rate how satisfied/dissatisfied you are with the frequency that you have to treat your HAE attacks*** (with respect to currently available treatments).

25.4% of patients (16 of 46) reported being *very dissatisfied or dissatisfied* with the frequency with which they had to treat their HAE attacks. A further 20.6% reported they were *neither satisfied/nor dissatisfied* with the frequency with which they had to treat their HAE attacks. Only 46% of patients reported being *satisfied/very satisfied* with the frequency with which they had to treat their HAE attacks.

Also, in the 2024 National Survey, patients were provided an opportunity to ***comment on their overall satisfaction with current HAE medications***.

The themes of these comments included: the need for more treatment options, medication that is easier to administer, and better, faster routes of administration. Concerns included having breakthrough attacks with current prophylaxis, activity limitations, cost of medication, stress of IV medication administration and anxiety about possible attacks. These themes reflect the complexity of managing HAE, balancing effective treatment with financial constraints, dealing with ongoing symptoms, and striving for a better quality of life.

Here is a sample of their comments in their own words.

-I would love to have more choices.
2024-07-17 08:18 p.m.

-I would like my doctor to let me try other things and take my HAE more seriously.

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2024-07-17 07:20 p.m.

-Easiest-to-self-administer meds are the most expensive. Lifetime financial limit makes me hesitant to use them.
2024-07-17 07:16 p.m.

-Now that I am on Orladeyo for long term prophylaxis and Berinert for acute attacks, I feel far less anxiety about attacks. I finally feel like we have an appropriate combination of medications.
2024-07-17 05:47 p.m.

-I continue to experience HAE symptoms despite being on Takhzyro but it is not clear if i'm reacting allergically to food and environmental triggers.
2024-07-01 10:33 p.m.

-My medication regime keeps me out of the hospital. But I want to be able to do more and not worry about swelling. Like get a job, exercise, be in the heat, be in the cold, play hard, give my husband a great birthday present without swelling... but I'm always holding back so I don't swell. I'm tired of being a boat anchor. I want to buy something with money I make
2024-06-30 11:58 p.m.

-I would like access to medication that is easier to administer. There is not equal access to treatment options in Canada like other G7 countries
2024-06-26 12:53 p.m.

-Having to give myself IVs is stressful especially when that part I'm poking is swelling . It is stressful leaving my home knowing I will have to find somewhere to do my iv or even just having to do an IV to begin with
2024-06-20 02:53 p.m.

-Berinert works, especially if given at first signs. I just need a better route/faster option such as Firazyr or a prophylactic medication.
2024-06-12 11:42 p.m.

-Would be nice if there were less attacks, but can live with how they are managed now
2024-06-12 10:45 p.m.

Conclusion: HAE patients urgently require prophylactic treatments that are more effective, convenient and easier to administer at home.

5. Improved Outcomes

Patients continue to seek treatments that better control attacks while offering greater convenience and ease of use. Treatments that eliminate or substantially reduce attacks compared to existing treatments are of critical importance to patients as each edema attack can be severely debilitating, and in many cases life-threatening.

Greater control of attacks would also ameliorate the ever-present anxiety and fear many patients experience due to unpredictable attacks and reduce the negative impact on a patient's ability to work, pursue education, travel, exercise, do household chores, and socialize with family and friends.

Further, HAE is a heterogeneous disease with complex pathophysiology. Current knowledge cannot provide convincing explanations for the clinical variability of the disease, or why some patients respond well to

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certain treatment and others do not. Consequently, more treatment options and innovative new treatments are urgently needed.

With respect to treatment innovation, garadacimab offers a novel mechanism of action whereby it inhibits the cascade of events leading to edema formation whereas other therapies target downstream mediators. Clinical trial results (and patient research conducted for this submission) also demonstrate that reduction in attacks is almost immediate once starting garadacimab. There is limited discomfort at the injection site (e.g., burning, redness) which is particularly important for those who are needle averse.

6. Experience With Drug Under Review

In July 2024, HAE Canada (HAEC) surveyed and interviewed patients who had experience with garadacimab. One patient provided a written response to the interview questions.

The key themes identified from the patient interviews about their experiences with HAE and garadacimab treatment included the following:

1. Treatment Efficacy:
    - All patients reported significant reductions or complete elimination of HAE attacks after starting garadacimab.
    - Prior treatments such as Berinert and other medications provided some relief but were not as effective as garadacimab.
    - Garadacimab was reported to prevent attacks even in situations that would typically trigger them.
2. Quality of Life Improvement:
    - Patients experienced a dramatic improvement in their quality of life, including the ability to live normally without the constant fear of attacks.
    - Many patients mentioned being able to resume or engage in activities that were previously impossible due to HAE.
    - Patients expressed deep gratitude for access to garadacimab and emphasized the life-changing impact it had on them.
3. Ease of Use and Convenience:
    - The once-monthly subcutaneous administration of garadacimab was found to be much more convenient compared to frequent IV treatments.
    - Patients appreciated the reduced need for emergency treatments and hospital visits.
4. Mental and Emotional Relief:
    - The reduction or elimination of attacks provided significant mental and emotional relief, reducing anxiety and stress related to HAE.
5. Side Effects:
    - Most patients reported minimal to no side effects from garadacimab.
    - Minor issues such as itching or slight swelling at the injection site were mentioned but considered manageable and insignificant compared to the benefits.
6. Challenges Before Garadacimab:
    - Before starting garadacimab, patients experienced frequent, painful, and sometimes life-threatening attacks.
    - Managing attacks often required complex and inconvenient treatments, which interfered with daily life and work responsibilities.

7. Impact on Family and Social Life:
    - The unpredictability of attacks placed a burden on patients' families and social interactions.
    - The effectiveness of garadacimab alleviated these burdens, allowing patients to engage more fully with their families and communities.
8. Hope for the Future:
    - Patients expressed hope for continued access to garadacimab and for its approval to help others suffering from HAE.
    - Patients expressed gratitude and hopefulness regarding their future and the future of their loved ones with HAE.
    - Several patients expressed a desire for their family members and others with HAE to have access to garadacimab.
    - There was a recurring theme of wanting a normal life for themselves and their children who have HAE.

Below are summaries of the patient interviews:

Patient AL (Interview date: July 12, 2024)

AL is a retired school administrator and has been experiencing HAE attacks since he was 17 years of age. His previous treatment was a C1 Esterase Inhibitor which he would administer when he felt an attack coming on. He would typically experience attacks in his extremities (limbs, hands, feet), gastrointestinal system, lips, tongue, and throat/larynx.

AL has been on treatment with garadacimab for approximately 3 years. He had over 12 attacks in the 12-month period prior to starting garadacimab. Since staring garadacimab, AL has had **ZERO** attacks. He reports that garadacimab has no noticeable side effects and is *"very tolerable"* and that garadacimab works very fast as it eliminated any HAE attacks immediately after commencing use. "*So far, I have not experienced any side effects. I feel healthy and don't have to suffer attacks…"*

AL told us that he had experienced many attacks since he was about 17. *"Most were very painful; others were also disabling, and some were life threatening and they occupied days and hours of my life. With garadacimab, I can live a normal life without all that suffering. I'm very grateful to have access to garadacimab. It makes my life so much better!"*

Patient BS (Interview date: July 15, 2024)

BS is a 71-year-old retired male with HAE.

Prior to starting the garadacimab trial, his treatment regimen would see him typically administer Berinert every 5 days to prevent attacks. If he extended that to 6 or 7 days, he would experience breakthrough attacks. Most of his attacks were in his abdomen. If he started to feel an attack coming on and treated it immediately, he reports that he could prevent the attack from manifesting. If he held off, then he would have to treat when symptoms started. He reports that it was tricky to (self) administer an IV treatment after symptoms started.

BS tells us that he used to have more than 12 attacks a year prior to starting garadacimab, but since starting the garadacimab trial, he has had "*NO ATTACKS"*. He has been on garadacimab since December 2021.

He further told us: *"Since starting the garadacimab trial I have had minor eye surgery, and dental work, both of which would have been triggers for an HAE attack, but while on garadacimab, there were NO attacks"*

He says that he still keeps Berinert on hand "*just in case"*, but that he has not had to use it since starting the garadacimab trial in December 2021. In fact, he reports that he took back six treatments of Berinert because they were unused/expired. (They are good for 2 years).

He told us: "*This treatment has changed my life."* He added: *"I have a son with HAE who uses Berinert, and I would love to see him get on garadacimab*."

Patient DL (Interview date: July 17, 2024)

DL is a 65-year-old female retired policy analyst with HAE. She was diagnosed with HAE sometime in her mid-30s and experienced a diagnostic odyssey with countless emergency room visits, admissions to the hospital and visits to doctors and specialists. She reports that she would go to the ER because she had "*vomiting and diarrhea that would go on for days"*. She reports that she would have many attacks while at work, and that these attacks would last a few days. Because she was not yet diagnosed with any specific disease/illness, sometimes her work colleagues would think she was *"faking"*. For her HAE attacks, DL would use up all her 1.25 sick days per month. She would then have to use all her vacation days. Her workplace eventually changed their sick day allotment to 7 days per year. This resulted in her exhausting her sick days and her vacation, resulting in her having to take unpaid days for some of her HAE attacks. DL also reports that because of her work absences and illness, she could not get life insurance.

Then, she was dating a young doctor who she says was *"smarter than most"* who correctly hypothesized that she had HAE and connected her with a physician who definitively diagnosed her with HAE. Eventually she had an HAE specialist in Ottawa that set up Berinert infusions for her at the General Hospital in Ottawa. Over time she was able to do the infusions with her husband's assistance at home. This was important to her as she lived 50 km from the hospital. When she divorced, she had to relearn how to do IV infusion herself, which she reports as being *"a big challenge".* She made a special effort to administer treatment early, at the first sign of an attack "*because I didn't want to have the extra difficulty and stress of trying to self-administer an IV when the attack got worse".*

DL started the garadacimab trial approximately 1.5 years ago. She reports that prior to garadacimab, she would treat attacks (when she felt them coming) with Berinert about 2-3 times per month. She reports that Berinert was effective if she treated early enough. And that *"if I waited too long, recovery was longer".*

After starting garadacimab, on one or two occasions, if she felt that an attack coming she would still administer Berinert. But she quickly realized that garadacimab was 100% effective at preventing attacks. While on garadacimab she has experienced NO attacks. She describes this as *"AMAZING"* and that garadacimab *"IS A LIFECHANGER".*

She reports that it is extremely easy to administer garadacimab compared to Berinert. Before *"I used to stress about missing the vein. Now there is no stress, no pain. I have a bit of itching/rash when doing SubQ in my abdomen, so I changed to doing it on my leg, and that is fine. I have some minor swelling that disappears rapidly. I would stick with therapy forever if I could. It has made my life so much easier."*

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DL further detailed her experience on therapy, and said she tried the rescue treatment Firazyr, which did not work for her. She says that her workplace benefits (drug insurance) paid over $100,000 for Firazyr in one year, leading her to fear that her private insurance was going to be cut off.

DL concluded her interview with HAEC by saying that *"I am 14 months attack free, which is something to celebrate. I also have a daughter on garadacimab, and she is also now attack free".*

Patient: KN (Interview date: July 16, 2024)

KN is a 40-year-old male, and has been a paramedic for 19 years

He was diagnosed with HAE when he was (approximately) 11 years old. He had HAE symptoms leading up to his diagnosis his whole life and recounts that he would go to the local hospital's emergency department countless times and that *"no one knew what the cause of his attacks was*" including his family doctor. Finally, he was referred to an HAE specialist who made a conclusive diagnosis.

KN has two children (who do not have HAE), and he has two sisters, one who has HAE, and his mother has HAE. He has nephews and nieces also with HAE.

KN describes his treatment regimen as follows: He would treat his attacks with Berinert (IV) when he felt an attack coming, or when he was fully experiencing an attack. KN says he would experience these attacks in his extremities (limbs, hands, feet) and in his gastrointestinal system.

KN was enrolled in the Vanguard study and started garadacimab approximately 9+ months ago. Prior to starting garadacimab he experienced HAE attacks 3 – 4 times per month. Since starting garadacimab he has experienced NO ATTACKS. He reports: "*For the first 2 months on garadacimab I had no attacks. I actually felt the early signs of an attack, but they never actually resulted in an attack. I still feel some early signs that previously would have meant an attack would be coming, but now, with garadacimab these attacks never manifest*". He added: "*The biggest difference for my life while taking garadacimab is actually NOT THINKING ABOUT having HAE or worrying about having an attack."* He also says that having to administer an IV treatment (Berinert) while at work was very inconvenient, and that the once-monthly subcutaneous treatment with garadacimab is "a breeze". He finds garadacimab to be very tolerable.

KN's reports that he is telling everyone in his family (who has HAE) about garadacimab and is hopeful that they will all have access to garadacimab.

KN related to HAEC that: *"In my younger years when treatment at a hospital was the only option I would often suffer through an attack because it was too inconvenient to get treatment. Garadacimab has been amazing so far. I almost forget sometimes that I have HAE."*

Patient: KM (Interview date: July 12, 2024)

KM is a retired social worker. Until her late teens, she had experienced a diagnostic odyssey. She was finally diagnosed with HAE during her first year at Queen's University, however, the first time she received treatment for HAE was at the age of 60. Her HAE attacks are typically in her abdomen.

Her first prescribed treatment was Berinert, but she required assistance to do home IV infusion, especially if the attack was severe/life-threatening. Not knowing when these attacks could occur caused KM extreme anxiety for her and her entire family and placed additional burdens on them to remain close and to work from home to support her care.

She eventually had access to Firazyr, a rescue medication that is administered subcutaneously. As such, her husband and daughter were both able to return to in-person work responsibilities as she no longer needed access to their support in the event of an attack. She also had been on Takhzyro (lanadelumab), but while she found that treatment reduced the frequency and severity of attacks, it was not totally effective, and there seem to be "*diminishing returns"* as time went on. During 2021, up until September 2021, KM HAD OVER 30 attacks. "*I was sick constantly. I was using Firazyr as a rescue medication a lot. The 30 attacks happened while I was still on Takhzyro*".

KM reports that when she started the garadacimab study, she noticed immediately that it was effective, and that she **has not had one attack** since starting on garadacimab.

She reports that administering garadacimab results in "*a little bit of stinging, which is no big deal at all. I get it in an auto injector. The prepared syringe was also easy, but the auto injector is extremely easy.*" She further reports that she has experienced no side effects from garadacimab. She also finds the once per month dosing to be extremely convenient. *"Once a month! I have it in my calendar."*

KM told us that garadacimab is "*the most effective treatment I have had. It gave me my life back at a time when I was needed by my elderly mom, who was still living in her condo and needed daily support. It was a stressful time, and I could not have pulled that off without the physical strength and stamina that garadacimab enabled. That kind of care giving is very demanding. Had I not been on garadacimab, I would not have been able to meet those demands in my life*."

Patient HN (Testimonial Date: July 26, 2024)

HN is a 32-year-old married mother of two children, one of whom also has HAE. She was diagnosed with HAE at the age of 5. In her childhood, the treatment she was offered for her HAE attacks was IV administered Benadryl and epinephrine. At the age of 21, she was prescribed Berinert which she said offered the *"first chance of relief"* from HAE attacks. She has been on the garadacimab for over 2 years.

HN reports that prior to her initial start to the garadacimab trial, she had been in the Orladeyo (APeX-2) study. While on that trial she had no relief from symptoms/attacks and discovered that she was on the placebo arm of the trial. Subsequently, the trial investigator removed her from that trial. After a washout period of 1 month, HN started the garadacimab trial. She says that this *"was the biggest transition and best decision of my life"* and that "*This medication has been my holy grail"*. HN tells us that garadacimab was rapidly effective, and that other than some stress-related early *"swells"* at the beginning of the trial, she has experienced a normal, attack-free life. HN tells us that prior to garadacimab she would have attacks *"like clockwork every 4 days"*. HN describes her life experiencing attacks every four days as *"never getting a break"* as HAE would *"interfere one way or another"* with her plans and everyday living.

She tells us that prior to starting garadacimab, being a mother with HAE was extremely difficult as she had to plan travels and vacation based on proximity to a hospital (for emergency administration of Berinert), and that she had to avoid many activities, such as riding a bike with her young children, as that would inevitably trigger an HAE attack/extreme genital swelling.

HN also tells us that the method of administration for garadacimab along with the once-monthly dosing schedule is a major convenience for her. She likens her experience of using intravenously administered Berinert as to being a *"pincushion"* and that subcutaneous garadacimab is much easier for her. She tells us that garadacimab *"has graced me with freedom, relief, and freedom of other treatments".*

She also tells us that *"I have not had to worry about any side effects".*

HN tells us that the last few years have been very stressful, with her husband having a heart attack in 2021, and she subsequently having had to pursue more demanding employment. She says that garadacimab has made getting through these last few years possible.

HN worries about access to garadacimab in the future. She says hopefully that *"The potential of this approval would then create a chance of normalcy with my daughter*" who she reports, was diagnosed with HAE at the age of one. HN hopes her daughter will have access to garadacimab and the opportunity for a normal life that garadacimab may provide. HN told us *"I really hope this drug gets approved. I know myself it's been the gift of medical bliss."*

SURVEY RESULTS

In our survey of patients who had experience with garadacimab, we asked: ***How many attacks did you experience in the 12 months prior to beginning garadacimab?***

0 attacks		**1-3 attacks**		**4-6 attacks**		**7-9 attacks**		**10-12 attacks**		**More than 12 attacks**		**Total**
8.33%	patients=1	8.33%	patients=1	16.67%	patients=2	0%	patients=0	0%	patients=0	66.67%	patients=8	N=12

We then asked: ***How many attacks did you experience in the 12 months after beginning garadacimab?***

0 attacks		**1-3 attacks**		**4-6 attacks**		**7-9 attacks**		**10-12 attacks**		**More than 12 attacks**		**Total**
58.3%	patients=7	33.33%	patients=4 *	8.33%	patients=1	0%	patients=0	0%	patients=0	0%	patients=0	N=12

***one patient reported feeling symptoms of an impending attack "one time" very early after starting garadacimab and took Berinert "one time" before it got worse.*

Observation: In the 12-month period prior to beginning garadacimab, over 66.67% of patients were experiencing more than 12 attacks. In the 12-month period after starting garadacimab, over 58.3% of patients did not experience **ANY** attacks. A further 33.33% of patients experienced 1-3 attacks in the 12-month period after starting garadacimab.

We asked patients: ***Based on personal experience with garadacimab, how would you rate its effectiveness in prevention of attacks of hereditary angioedema? 1 is "not effective" and 5 is "extremely effective".***

91.67% (n=11) of patients rated garadacimab as being “Extremely Effective”, with 8.33% of patients (n=1) rating garadacimab as being “4” (very effective).

We asked patients: ***Based on your personal experience with garadacimab, how would you rate its side effects? 1 is "completely intolerable" and 5 is "very tolerable".***

Rate garadacimab’s ***side effects 1 is "completely intolerable" and 5 is "very tolerable".***						
1 (completely intolerable)	**2**	**3**	**4**	**5 (very tolerable)**	**N/A**	**Weighted Average (WA)**
1pt (9.09%)	0pts (0%)	1pt (9.09%)	1pt (9.09%)	7pts (63.64%)	1pt (9.09%)	**4.30**

We asked patients: ***In general, how would you rate the speed at which garadacimab noticeably began reducing HAE attacks compared to other treatments you have used for the prevention of HAE attacks? 1 is "garadacimab is much slower" and 5 is "garadacimab is much faster".***

Rate the speed at which ***garadacimab noticeably began reducing HAE attacks (compared to other treatments) 1 is "garadacimab is much slower” and 5 is "garadacimab is much faster".***						
1 (*garadacimab is much slower*)	**2**	**3**	**4**	**5 (garadacimab is much faster)**	**N/A**	**Weighted Average (WA)**
0pt (0%)	1pts (8.33%)	1pt (8.33%)	3pt (25%)	6pts (50%)	1pt (8.33%)	**4.27**

We asked: ***On a scale of 1-5 how would you rate your quality of life while taking garadacimab? 1 is "low/seriously impacted", and 5 is "high/normal living".***

Rate your quality of life while taking ***garadacimab. 1 is "low/seriously impacted” and 5 is "high/normal living”***						
1 (*low/seriously impacted*)	**2**	**3**	**4**	**5 (*high/normal living*)**	**N/A**	**Weighted Average (WA)**
0pt (0%)	0pt (0%)	0pt (0%)	2pts (16.67%)	10pts (83.33%)	0pt (0%)	**4.83**

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We asked: ***What are the side effects that you have experienced with garadacimab. Rate them on a scale of 1 - 5. 1 is "completely intolerable" and 5 is "very tolerable".***

	1 - COMPLETELY INTOLERABLE (1)	2 (2)	3 (3)	4 (4)	5 - VERY TOLERABLE (5)	N/A	TOTAL	WEIGHTED AVERAGE
abdominal pain	9.1% 1	0.0% 0	0.0% 0	9.1% 1	18.2% 2	63.6% 7	11	3.75
diarrhea	9.1% 1	0.0% 0	0.0% 0	0.0% 0	18.2% 2	72.7% 8	11	3.67
nausea/vomiting	9.1% 1	0.0% 0	0.0% 0	0.0% 0	18.2% 2	72.7% 8	11	3.67
back pain	9.1% 1	0.0% 0	0.0% 0	0.0% 0	18.2% 2	72.7% 8	11	3.67
heartburn.	0.0% 0	9.1% 1	0.0% 0	0.0% 0	18.2% 2	72.7% 8	11	4.00
injection site pain/itching	9.1% 1	9.1% 1	0.0% 0	9.1% 1	45.5% 5	27.3% 3	11	4.00
respiratory tract infection	0.0% 0	9.1% 1	9.1% 1	0.0% 0	18.2% 2	63.6% 7	11	3.75
nasopharyngitis (a cold)	8.3% 1	0.0% 0	8.3% 1	8.3% 1	25.0% 3	50.0% 6	12	3.83

We asked: ***Based on your personal experience with garadacimab, how does it compare in terms of side effects to the other therapies you have taken for the prevention of HAE attacks? Rate on a scale of 1 - 5. 1 is "much harder to tolerate" and 5 is "much easier to tolerate".***

	1 - MUCH HARDER TO TOLERATE	2	3	4	5 - MUCH EASIER TO TOLERATE	N/A	TOTAL	WEIGHTED AVERAGE
Cinryze (complement C1 esterase inhibitor)	0.0% 0	0.0% 0	0.0% 0	0.0% 0	9.1% 1	90.9% 10	11	5.00
Haegarda (c1 esterase inhibitor subcutaneous [human] injection)	0.0% 0	8.3% 1	8.3% 1	0.0% 0	16.7% 2	66.7% 8	12	3.75
Berinert (C1 Esterase Inhibitor [human])	0.0% 0	9.1% 1	18.2% 2	18.2% 2	18.2% 2	36.4% 4	11	3.71
Takhzyro (lanadelumab)	0.0% 0	0.0% 0	0.0% 0	9.1% 1	9.1% 1	81.8% 9	11	4.50
Orladeyo (berotralstat)	0.0% 0	0.0% 0	0.0% 0	0.0% 0	27.3% 3	72.7% 8	11	5.00
Tranexamic acid	9.1% 1	0.0% 0	0.0% 0	9.1% 1	9.1% 1	72.7% 8	11	3.33
Danazol	0.0% 0	0.0% 0	0.0% 0	10.0% 1	0.0% 0	90.0% 9	10	4.00

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We asked patients: ***Is there anything else about garadacimab that you would like us to know and include?***

Here are the responses provided by some patients:

*-Has been a life saver, got my life back …. rode my bike for the first time in like 8 yrs once I started the dosing, as it would cause a swell. Been able to do so much more and not think oh f*** is this going to cause a swell and not do it because of the unwanting need to administer Berinert again and regardless was having a flare up every 4 days and having to carry an obnoxious amount of medication on hand for my dosing. The stress and worry took a major weight of my shoulders and think what happens if I don't catch it(husband works away and we have 2 kids (10 and 8) I could die and leave them with trauma and issues*
2024-07-07 08:25 p.m.

-Best HAE treatment so far. It's as if I don't have HAE anymore
2024-07-04 09:09 a.m.

-Easy to adjust treatment dates, +or- 4days per month. Very easy to travel with. Fast and easy to administer vs other products. Fewer peripherals required as per other treatment products.
2024-07-03 11:46 p.m.

-Of all the studies and treatments I have participated in/had this is by far the best.
2024-07-03 03:34 p.m.

We asked: ***How has garadacimab changed, or how is it expected to change your long-term health and well-being?***

Here are the responses provided by some patients:

-Life is easy! (Hae wise) and worry thrown to the wind 1 dose, once a month has given me over 2 years of bliss. Knowing the trial is coming to an end petrifies me.
2024-07-07 08:25 p.m.

-It has brought enormous relief from the constant anxiety of frequent HAE episodes which completely disrupted normal life/activities. The suffering involved was a huge burden.
2024-07-04 10:40 a.m.

-Health is much better
2024-07-04 09:09 a.m.

-No attacks!
2024-07-03 11:46 p.m.

-So far, I've not experienced any side effects. I feel healthy and don't have to suffer attacks every week or so. Should I expect any changes in the long term?
2024-07-03 05:35 p.m.

-I hope I can stay on it forever. I am a part of a study so I don't know what will happen once the study is over.
2024-07-03 03:34 p.m.

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We also asked: ***Can you tell us about your story and why access to garadacimab and future therapies are so important to you?***

-I can lead a normal life. No need to worry about my next attack. Can do all activities.
2024-07-04 09:09 a.m.

-After many years of continuing HAE attacks, lost work/schools day and family functions. It is nice to know that I will not have HAE attacks. As well, it would be nice to have other family members with HAE and other HAE patients experience the same HAE attack free life and ease of treatment to prevent attacks.
2024-07-03 11:46 p.m.

-I have experienced many attacks since I was about 17…. with garadacimab, I can live a normal life …I'm very grateful to have access to garadacimab and makes my life so much better!!
2024-07-03 05:35 p.m.

-I am a paramedic Superintendent who works shift work. I am a father of 2 (5 and 3 years old). In general, I am a pretty active and busy person. I have been dealing with HAE my whole life. In my younger years when treatment at a hospital was the only option I would often suffer through an attack because it was too inconvenient to get treatment. Garadacimab has been amazing so far. I almost forget sometimes that I have HAE.
2024-07-03 03:34 p.m.

Conclusion:

Garadacimab is an extremely effective prophylactic medication for many patients. The percentage of patients who report that garadacimab has completely or mostly eliminated their HAE attacks is remarkable. Further, patients with experience with garadacimab overwhelmingly report that it is easy to tolerate. Patients are also highly satisfied with the convenience of the subcutaneous administration (vs. IV administration) and are also highly satisfied with the dosing schedule (once monthly). HAE Canada deems it to be extremely urgent that garadacimab be made available to Canadian patients with HAE.

HAE Canada has never observed such patient enthusiasm and satisfaction with a new treatment.

7. Companion Diagnostic Test

The identification of biomarkers and development of accompanying bioassays are urgently needed to accompany clinical trials and enable personalized medicine for HAE. Biomarkers are sought because they can be utilized to diagnose, guide therapies, or make predictions regarding the clinical course of HAE.

HAE Canada encourages ongoing research to identify and validate biomarkers for HAE, and to monitor these biomarkers longitudinally to determine their clinical utility and predictive value.

8. Anything Else?

HAE is a heterogeneous disease with complex pathophysiology. Current knowledge cannot provide convincing explanations for the clinical variability of the disease, and despite detailed research and identification of novel defects, for a large percentage of patients with HAE, the genetic cause is unknown (HAE-UNK). More research work is required to uncover different disease endotypes to identify specified targets for therapeutic intervention with the goal of more effective, individualized management of the disease.

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Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   HAE Canada used regular and contracted employee assistance to conduct research and complete this submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   The collection and analysis of data was accomplished exclusively using HAE Canada resources and tools. Both regular and contracted staff participated in data collection and analysis efforts

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BioCryst				x
Astria			x	
CSL Behring				x
KalVista			x	
Pharvaris			x	
Takeda Canada				x

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Daphne Dumbrille
Position: COO
Patient Group: HAE Canada: Advocacy Committee and Board of Directors
Date: July 31, 2024

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CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0860-000
Generic Drug Name (Brand Name): garadacimab
Indication: Hereditary Angioedema (HAE)
Name of Clinician Group: Canadian Hereditary Angioedema Network (CHAEN)
Author of Submission: Dr. Amin Kanani with the CHAEN Board of Directors

The CHAEN Board of Directors:

Chair: Dr. Stephen Betschel, Clinical Immunologist and Allergist, Unity Health - St. Michael's Hospital
Dr. Rozita Borici-Mazi, Allergy and Immunology, Oxford Allergy Clinic, London, Ontario.
Dr Hugo Chapdelaine, Adult Clinical Immunology Clinic, Montreal Clinical Research Institute
Dr. Dawn Goodyear, Associate Professor, University of Calgary
Dr. Chrystyna Kalicinsky, Department of Internal Medicine, University of Manitoba
Dr. Amin Kanani, Division of Allergy and Clinical Immunology, St. Paul's Hospital, Department of Medicine, University of British Columbia
Dr. Paul Keith, Department of Medicine, McMaster University
Dr. Gina Lacuesta, Department of Medicine, Dalhousie University
Dr. Susan Waserman, Department of Medicine, McMaster University

1. About Your Clinician Group

The Canadian Hereditary Angioedema Network (CHAEN) is an organization of physicians who treat and/or are interested in Hereditary Angioedema, and who contribute to the knowledge of HAE and its treatments, including participating in clinical trials, conducting observational research, and involvement in local/provincial and national clinical guideline development and health technology assessment. Our vision is to enable HAE patients in Canada to receive appropriate support and care so that they can live full lives. CHAEN is incorporated under the Canada Not-For-Profit Corporations Act.

https://chaen-rcah.ca/

2. Information Gathering

Information was gathered through personal experience in treating patients with hereditary angioedema, literature review, participation as investigators in clinical trials, and virtual discussion among experts.

The contributors to this submission are familiar with the VANGUARD study, a pivotal, multicentre, randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of once-monthly subcutaneous administrations of garadacimab as prophylaxis for hereditary angioedema. The VANGUARD study recruited patients (aged ≥12 years) with type I or type II hereditary angioedema across seven countries including Canada.

3. Current Treatments and Treatment Goals

HAE can be categorized into 3 different types including HAE with deficient C1-inhibitor levels (HAE-1), HAE with dysfunctional C1-inhibitor (HAE-2), and HAE with normal C1-inhibitor function (HAE nC1-INH) previously referred to as type 3. For the purposes of this submission, we are focusing on currently available treatments in Canada for HAE-1 and HAE-2 that are for long-term prophylaxis (LTP), which involves initiating continuous regular treatment aimed at minimizing the number, frequency, and severity of attacks.

For the Long-Term Prophylaxis of HAE Attacks, the treatments available in Canada are:

- C1-INH concentrate - human (Cinryze), which is a plasma-derived treatment administered intravenously
- C1-INH concentrate - human (Haegarda) which is a plasma-derived treatment administered subcutaneously
- Lanadelumab (Takhzyro) - Human monoclonal antibody which is administered subcutaneously
- Berotralstat (Orladeyo) - which is a plasma kallikrein inhibitor which is taken orally once daily.

The ultimate goal for an HAE treatment is to achieve no angioedema attacks, and to achieve total control of the disease and normalize the patient's life. Recognizing the burden to patients associated with HAE, including the ever-present risk of experiencing a life-threatening laryngeal attack, the impact of HAE on a person’s health-related quality of life (HRQoL) can be considerable. Thus, improved preventative treatments are urgently needed. Patients continue to seek treatments that better control attacks while offering greater convenience and ease of use.

Further, IV treatments have the effect of requiring patients to spend much time traveling to treatment and undergoing treatment; especially if they have difficulty doing home infusions.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Certain current prophylactic treatments for HAE do not provide early or sustained protection against attacks and may require frequent dosing. There is an unmet need for more convenient, well-tolerated, prophylactic treatments that show proven early and sustained efficacy in reducing the number and severity of HAE attacks, with a rapid onset of protection.

Patients also require more convenient methods/modalities of self-administration (vs. Intravenous self-administration or intravenous administration at an infusion clinic).

Different treatment choices are vital also to ensure patients have options when they are faced with drug shortages, which is currently a reality and potentially will continue to be in the future. Ensuring the availability of optional treatments is particularly important when dealing with a potentially life-threatening condition.

HAE patients need prophylactic treatments that can safely be taken regularly for years or even decades.

Patients that may have the greatest unmet need for an intervention such as garadacimab are:

- Patients who find current prophylactic treatments to be ineffective, or slow to take effect
- Patients who are experiencing side effects from current therapies
- Patients who experience damage to their veins, or worry about future damage to their veins
- Patients who find it difficult and uncomfortable to self-administer intravenous prophylactic treatments for HAE
- Patients who live far away from hospital care
- Patients concerned about risk of infectious agent transmission and supply interruptions / shortages from plasma-derived HAE treatments
- Patients who travel frequently, and require a treatment that is easy to transport, does not require complicated reconstitution, and is easy to administer

For many patients, Garadacimab has the potential to fill the unmet needs detailed above.

Of particular note, is the early onset of protection with garadacimab. Nearly three-quarters of patients in the Vanguard trial were attack-free within the first 3 months, and had sustained efficacy over the second 3-month period.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

To improve patient quality of life, reducing the treatment burden of HAE prophylaxis is an important consideration. A safe and effective non-plasma derived subcutaneously administered treatment may be preferred to an intravenously administered plasma-derived treatment by some patients.

For instance, some patients may be on anticoagulation/ASA who experience easy bruising due to current HAE treatments and there may be patients who won't use blood products. Younger patients who meet the age indication for garadacimab may see a once-monthly administration to be much more convenient given the difficulties and aversions associated with more frequent intravenously administered therapy for this demographic.

Because garadacimab is given subcutaneously and once per month, it is associated with a lower treatment burden compared to infused plasma derived C1 inhibitor.

Garadacimab has a smaller injection volume compared to other subcutaneous therapies, making it better tolerated with fewer local side effects. Importantly, garadacimab is a novel, first-in-class, recombinant monoclonal antibody targeting activated FXII. FXIIa is a plasma protein that initiates the kallikrein-kinin cascade of HAE attacks. By targeting FXIIa, garadacimab inhibits this cascade at the top as compared to HAE therapies that target downstream mediators.

The aim of long-term prophylaxis is to reduce the frequency and/or severity of attacks of HAE and minimize the impact of HAE on QoL, thereby enabling patients to live normal lives. Patients who are candidates for long-term therapy with garadacimab should explore with their treating physician the benefits and risks associated with garadacimab to optimize patient care.

It is important to remember that no prophylactic regimen has been associated with the complete elimination of angioedema. Therefore, despite being on prophylaxis, all patients should be equipped to treat angioedema attacks and an acute treatment plan should be agreed to between patient and physician.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

This treatment should be considered along with other currently available treatments for long-term prophylaxis with patient preference contributing to the ultimate treatment choice. All patients who are candidates for LTP should be made aware of this new treatment option.

Additionally, for patients who travel frequently, or who find their current treatment to be difficult to administer, this treatment offers tremendous convenience as it is administered subcutaneously once per month.

Long term prophylaxis (LTP) is considered at every follow up visit for HAE patients. Shared decision making between patient and clinician occurs and once the patient is ready for LTP- all LTP options are discussed, and again shared decision-making occurs to find the best treatment option for that patient. Those patients

already on LTP, would also have a review at each follow up visit, to see if a switch in treatment would be potentially beneficial for that patient. There currently is no data on use of garadacimab during pregnancy.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The outcomes used in clinical practice align with the outcomes used in clinical trials. Clinical follow-up includes: review of number and severity of attacks, requirement for on demand acute therapy, emergency room visits and hospitalization. Some clinics will use angioedema control scores and health related QoL scores. Side effects would also be monitored

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Considerations leading to treatment discontinuation include:

- ineffectiveness (poor control of HAE with increased or continued attack frequency and severity)
- side effects,

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

As the treatment under review (garadacimab) is a once-monthly subcutaneous treatment, administration at home is an appropriate setting.

6. Additional Information

Canadian Blood Services (CBS) has identified the decrease in the percentage of plasma-derived products delivered to Canadian patients that are produced from plasma collected at Canadian donor centres as a material risk needing mitigation. CBS further identifies that globally, the use and demand for plasma-derived therapies continue to rise.

The standard -of-care treatment for HAE is plasma derived C1 esterase inhibitor concentrate, which is prepared from large pools of human plasma. While CBS has the goal of collecting more plasma domestically to help mitigate plasma supply issues, an important strategy to mitigate demand of plasma-derived therapies is to also offer patients non-plasma derived therapies when such therapies offer required efficacy, safety and convenience.

Further, product safety as it relates to risk of infectious agent transmission from plasma-derived products, remains a concern with some patients. Although multiple critical steps are taken to minimize the risk of infection from transfusion of blood products, this remains top-of-mind for certain patients driving their preference for non-plasma derived treatments.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   NO

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   NO

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Amin Kanani

Name: Amin Kanani
Position: Division Head, Allergy and Immunology, University of British Columbia
Date: 22/07/2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Takeda		X		
CSL Behring		X		
Biocryst		X		
Canadian Hereditary Angioedema Network		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Gina Lacuesta

Name: Gina Lacuesta
Position: Physician, Allergist and Clinical Immunologist
Date: 22-07-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Biocryst		x		
Takeda		x		
CSL Behring		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Dawn Goodyear

Name: Dawn Goodyear
Position: Associate Professor, University of Calgary
Date: 04-07-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Takeda			x	
BioCryst		x		
CSL Behring		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Hugo Chapdelaine

Name: Hugo Chapdelaine
Position: Adult Clinical Immunology Clinic, Montreal Clinical Research Institute
Date: 07-24-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Takeda		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Stephen Betchel

Name: Stephen Betchel
Position: Clinical Immunologist and Allergist, Unity Health - St. Michael's Hospital
Date: 07-26-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Astria	x			
Biocryst		x		
CSL Behring			x	
Ionis	x			
Pharvaris		x		
Takeda			x	
Kalvista			x	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Paul Keith

Name: Paul Keith
Position: Department of Medicine, McMaster University
Date: 07-26-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
CSL Behring				x
Biocryst		x		

Declaration for Susan Waserman

Name: Susan Waserman
Position: Department of Medicine, McMaster University
Date: 07-26-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Astria				
Biocryst	x			
CSL Behring	x			
Pfizer		x		

Declaration for Rozita Borici-Mazi

Name: Rozita Borici-Mazi
Position: Specialist in Allergy and Clinical Immunology /Oxford Allergy Clinic, London Ontario
Date: August 1, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Takeda		x		
CSL Behring		x		

Declaration for Chrystyna Kalicinsky

Name: Dr. Chrystyna Kalicinsky
Position: Clinical Allergist and Immunologist
Date: July 29, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Takeda	x			
CSL Behring	x			
Biocryst	x			