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Letter to the Editor

Andembry (Garadacimab-gxii): A Novel Monoclonal Antibody for Preventing Hereditary Angioedema Attacks

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Abstract

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent, potentially life-threatening episodes of angioedema affecting the skin, gastrointestinal tract, and airway. It results from dysregulation of the kallikrein–kinin system due to C1-esterase inhibitor deficiency or dysfunction, leading to excessive bradykinin production and increased vascular permeability. Despite advances in prophylactic therapies such as C1-INH replacement, kallikrein inhibitors, and bradykinin receptor antagonists, limitations including frequent dosing, breakthrough attacks, and variable response, remain. Garadacimab is a novel fully human monoclonal antibody that targets activated factor XII (FXIIa), inhibiting initiation of the contact activation pathway upstream of bradykinin generation. Blocking FXIIa, it prevents prekallikrein activation and downstream inflammatory cascade amplification. Clinical trials across Phase 1–3 studies demonstrate consistent pharmacodynamic target engagement, dose-dependent suppression of the kallikrein pathway, and significant reductions in attack rates, with a substantial proportion of patients remaining attack-free. The pivotal Phase 3 (VANGUARD) study further confirmed sustained efficacy and meaningful improvements in health-related quality of life. Garadacimab has shown a favorable safety profile, with mostly mild to moderate adverse events and no major safety concerns. Its long half-life enables once-monthly subcutaneous administration, potentially improving adherence and reducing treatment burden compared with existing therapies. Overall, FXIIa inhibition with Garadacimab represents a promising upstream prophylactic strategy for HAE, addressing key limitations of current treatments and offering durable disease control. Further real-world and comparative studies are needed to define its long-term role in clinical practice and broader applicability in contact system–mediated disorders.

More Information

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Introduction

Hereditary angioedema (HAE) is an autosomal dominant condition marked by recurrent episodes of intense swelling, most commonly involving the limbs, face, gastrointestinal tract, and airways. HAE symptoms usually begin in childhood and worsen during adolescence, with attack frequency and severity varying by individual. Episodes may be triggered by stress or trauma, but often occur without cause. While swelling typically resolves on its own, airway involvement can be life-threatening [1]. The underlying pathophysiology involves a dysfunction of C1 esterase inhibitor (C1-INH), leading to unchecked activation of the kallikrein-kinin system and excessive production of bradykinin, a potent vasodilator responsible for increased vascular permeability and edema. While current therapeutic options including C1-INH replacement, bradykinin receptor antagonists, and plasma kallikrein inhibitors, have significantly improved disease control, they are often associated with limitations such as frequent administration, breakthrough attacks, and variable patient response. Garadacimab, a fully human monoclonal antibody targeting activated factor XII (FXIIa), represents a novel therapeutic strategy aimed at preventing the initiation of the kallikrein-bradykinin cascade upstream. Clinical studies suggest that Garadacimab may offer effective prophylaxis with a favorable safety profile [2].

The U.S. FDA granted marketing approval for Garadacimab-gxii (trade name: Andembry) on June 16, 2025, for the prophylactic treatment of HAE.

This letter aims to explore the potential of Garadacimab as a prophylactic treatment in patients with HAE and to evaluate its clinical impact in addressing the unmet needs in HAE management.

Mechanism of action

Garadacimab's mechanism of action involves binding to the catalytic domain of activated factor XII (FXIIa). FXII is the first factor activated in the contact system. A circulating plasma protein called high-molecular-weight kininogen (HMWK or HK) aids in the initiation of the blood coagulation cascade. Plasma kallikrein, a zymogen precursor, is activated during contact system activation, cleaving HMWK to release bradykinin, a potent vasodilator. In vivo, FXIIa initiates the kallikrein-kinin system, triggering angioedema. It is involved in various physiological pathways, including prothrombotic and proinflammatory processes [3]. Garadacimab binds to βFXIIa through an extremely long CDR-H3 that inserts into the S1 pocket in a non-recognized habit. CDR H3 is the most diverse region in antibodies, and frequently contributes significantly to binding strength and plays a key role in antigen recognition. This is the reason for the restriction of triggered FXIIa proteolytic activity in HAE. The inhibition of FXIIa therefore prevents the activation of prekallikrein into kallikrein and the generation of bradykinin responsible for causing angioedema [4].

Clinical research evidence

The clinical development program of Garadacimab demonstrates a stepwise evaluation from early pharmacodynamic validation to large-scale efficacy confirmation in hereditary angioedema prophylaxis. Across Phase 1–3 studies, consistent suppression of FXIIa-mediated pathway activity and corresponding reductions in angioedema attack rates have been observed, supporting its upstream mechanism of action. Several clinical trials have been run on Garadacimab, a first-in-class anti-FXIIa agent for HAE prophylaxis. It showed a dose-dependent increase in plasma concentration in a Phase 1 study in healthy adult males. It successfully targeted FXIIa, inhibiting downstream Protein Kinase A (PKa) activity and prolonging activated Partial Thromboplastin Time (aPTT) [5]. These findings confirmed target engagement through FXIIa inhibition and demonstrated dose-dependent pharmacodynamic effects consistent with pathway modulation.

A Phase 2 double-blind, placebo-controlled, randomized study found that 88% of Garadacimab 200 mg-treated patients remained attack-free throughout the 12-week treatment period. *Ex vivo* assays revealed that Garadacimab inhibited FXIIa-mediated PKa activity in a dose-dependent manner, confirming the findings of the Phase 1 study. The study provided the first clinical evidence for therapeutic targeting of FXIIa for HAE patients [6]. These findings provided early proof-of-concept that upstream inhibition of FXIIa can translate into a clinically meaningful reduction in HAE attack frequency, establishing biological plausibility for this therapeutic approach.

The Phase 3 (VANGUARD) study of Garadacimab, a drug used to treat HAE-C1INH, found that it significantly reduced the number of attacks and remained attack-free for 62% of patients compared to the placebo group. Additionally, 77% of patients in the Garadacimab group had no attacks for at least 72 days from the first dose. This demonstrated the long-term efficacy of targeting FXIIa and improved Health Related Quality of Life (HRQoL), as assessed by the Angioedema-Quality of Life Questionnaire (AE-QoL) [7]. The Phase 3 findings further reinforced the durability of effect, demonstrating sustained attack prevention and clinically meaningful improvements in health-related quality of life, supporting its role as a long-term prophylactic therapy.

Collectively, the Phase 1–3 program demonstrates a consistent translational link between FXIIa inhibition, downstream kallikrein pathway suppression, and reduction in clinical attack burden in HAE.

Comparison with existing therapies

Current prophylactic therapies for HAE primarily target downstream components of the kallikrein–kinin cascade, whereas emerging therapies such as Garadacimab act at an upstream activation point, potentially preventing cascade initiation rather than modulating its downstream effects. The existing treatment strategies for managing HAE are: on-demand treatment (ODT), which lessens the severity and duration of attacks; short-term prophylaxis, which reduces the risk of attacks before triggering events like dental or surgical procedures; and long-term prophylaxis (LTP), which is the regular use of medication to lower the burden of disease by preventing attacks. First-line treatments for kallikrein-kinin system disorders target components, with C1-INH therapy being recommended for supplementing deficient or dysfunctional C1-INH. Other first-line treatments include ecallantide, icatibant, lanadelumab, and berotralstat [8,9]. While these agents effectively reduce bradykinin generation or receptor activation, they act at later stages of the pathway, requiring ongoing suppression of already activated inflammatory mediators. Unlike C1-INH, lanadelumab, or berotralstat, which act later in the cascade (e.g., at kallikrein or bradykinin), Garadacimab blocks Factor XIIa, preventing the entire downstream activation of kallikrein and bradykinin. By targeting Factor XIIa, Garadacimab intervenes at the earliest identifiable step in the contact activation pathway, thereby preventing amplification of downstream kallikrein and bradykinin production. Gradacimab's long half-life allows for monthly subcutaneous delivery, in contrast to lanadelumab, which

needs to be administered every two weeks via injection or every day by oral berotralstat [5]. This reduction in dosing frequency may improve treatment adherence and reduce overall treatment burden in long-term prophylaxis settings. The exact cost of the drug in the U.S. and Europe has not yet been publicly disclosed in official sources, as it is newly launched and long-term modeling and health-technology assessments are required.

Overall, Garadacimab represents a mechanistically upstream prophylactic strategy compared with existing therapies that primarily act at the level of kallikrein inhibition or bradykinin receptor blockade.

Safety and patient-reported outcomes

Moreover, Garadacimab's safety profile was first tested in cynomolgus monkeys, showing an acceptable tolerability profile [10]. Phase 2 and pivotal Phase 3 studies validated this, demonstrating a consistent and favorable safety profile in patients with HAE. Adverse events were mild or moderate, with no significant events [6,7]. A study found no abnormal bleeding events related to Garadacimab in severe COVID-19 patients, despite one-third receiving concurrent anticoagulant therapy [11].

Of special importance is the fact that Garadacimab is a good option for helping patients reach the objective of total illness control because of its long-lasting effectiveness, high percentage of patients who remain attack-free, high patient satisfaction, and the ease of a monthly fixed dose via SC self-administration. Many individuals in clinical trials saw a significant decrease in attack rates, and others even stopped having attacks altogether. According to metrics such as the AE-QoL and the Subject's Global Assessment of Response to Therapy (SGART), patients who received Garadacimab reported increases in their general quality of life. Interestingly, no thromboembolic or aberrant bleeding episodes have been reported in clinical trials. On the contrary, treatment-emergent adverse events such as upper-respiratory tract infections, nasopharyngitis, and stomach pain were the most common. Pain, itching, swelling, or redness near the injection site was also observed [5,12].

Future research directions

Despite promising clinical outcomes, several key knowledge gaps remain regarding the long-term positioning of FXIIa inhibition in hereditary angioedema management. Extended real-world data are required to confirm sustained efficacy, durability of attack prevention, and long-term safety beyond controlled trial settings. In particular, head-to-head comparative studies with existing long-term prophylactic agents such as C1-INH replacement therapies, lanadelumab, and berotralstat are needed to define relative efficacy, optimal patient selection, and sequencing within treatment algorithms.

Henceforth, future research should focus on enhancing our knowledge of FXIIa inhibitors' therapeutic potential in HAE-nC1INH patients, comparing long-term results and optimizing therapy approaches. FXIIa inhibition may help manage comorbidities in patients with HAE, including thromboembolic, proinflammatory, and autoimmune diseases. Future studies should explore whether Garadacimab's thromboprotective effect is replicated in patients at high thrombosis risk or in conditions where conventional anticoagulants are not feasible. Garadacimab's efficacy in HAE raises the possibility that FXIIa inhibition could have broader therapeutic relevance, but this remains speculative and requires further investigation [3,13].

Conclusion

Taking all the evidence presented into account, Andembry (Garadacimab-gxii) represents a targeted and innovative therapeutic option for the prophylactic management of HAE. Its long-acting mechanism of action, convenient administration, and ability to selectively inhibit factor XII highlight its potential as a cornerstone in long-term HAE prevention. It not only down-regulates the kallikrein-bradykinin cascade but also offers a reduction in sensitivity to known triggers of kallikrein activation. In addition, exploratory studies have suggested potential broader applications of FXIIa inhibition beyond hereditary angioedema, although these remain to be clinically established. Standardized treatment protocols and integration guidelines will reinforce Garadacimab's position as a valuable agent in disease control, reduction of attack frequency, and overall improvement of quality of life for HAE patients worldwide [7,11,14].

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