Clinical Evidence With Garadacimab Demonstrates No Impact on Hemostasis

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CONCLUSIONS

- Clinical evidence from the hereditary angioedema (HAE) and COVID-19 studies demonstrated that garadacimab had no impact on hemostasis
- Additionally, no impact was observed with garadacimab co-administered with hemostasis-impacting treatments in patients with COVID-19
- These clinical observations align with data supporting the absence of a bleeding phenotype in patients with a congenital factor XII (FXII) deficiency

BACKGROUND

FXII and the contact system

- Activated FXII (FXIIa) is the initiator of the contact system, encompassing the kallikrein–kinin system and the intrinsic coagulation system[1]
- FXII deficiency does not impact hemostasis *in vivo,* and patients with a congenital FXII deficiency have no increased risk of bleeding[2,3]

Targeting FXIIa with garadacimab in patients with HAE

- Initiation of the kallikrein–kinin system by FXIIa results in bradykinin production, the principal mediator of HAE; thus, inhibition of FXIIa is an attractive strategy for HAE prophylaxis[4,5]
- Garadacimab (first-in-class, fully human anti-FXIIa antibody) has shown durable and early onset of protection against HAE attacks with a favorable long-term safety profile in Phase 3 studies[6-9]

Targeting FXIIa with garadacimab in patients with COVID-19

- Indirect evidence suggests FXII-related pathways may be involved in pathophysiologic responses to COVID-19[10]
- Garadacimab efficacy and safety were assessed in a Phase 2 study in patients hospitalized with severe COVID-19 during the pandemic[10]

Safety across the garadacimab clinical program

- Due to the role of FXII in the contact system, abnormal bleeding and thromboembolic events were monitored as adverse events of special interest (AESIs per protocol) in the Phase 2 and Phase 3 HAE studies and in the Phase 2 COVID-19 study[6-10]

OBJECTIVE

- To assess the potential impact of FXIIa inhibition by garadacimab on hemostasis in patients with HAE and with COVID-19, including patients who were co-administered treatments impacting hemostasis

METHODS

SMQ evaluation of potential impact on hemostasis in garadacimab HAE clinical studies

HAE clinical program

- **Phase 2 study (N=32)**[7]: 75, 200 or 600 mg SC q1m (n=24); placebo (n=8)
- **Pivotal Phase 3 (VANGUARD) study (N=64)**[6]: 200 mg SC q1m (n=39); placebo (n=25)
- **Phase 3 OLE study (N=161)**[9]: 200 mg SC q1m

SMQ

Query: "hemorrhages"

Signal-detection tool identifying potential abnormal bleeding AEs by retrieving "hits" of grouped MedDRA terms

Medical evaluation of SMQ-identified hits*

- Clinical context
- Relatedness
- Company assessment
- Review of investigator assessment

Garadacimab with concomitant hemostasis-impacting treatment AE assessment

HAE clinical program

- **Phase 2 study (N=32)**[7]: 75, 200 or 600 mg SC q1m (n=24); placebo (n=8)
- **Pivotal Phase 3 (VANGUARD) study (N=64)**[6]: 200 mg SC q1m (n=39); placebo (n=25); 6-month treatment
- **Phase 3 OLE study (N=161)**[9]: 200 mg SC q1m; ≥12-month treatment†

COVID-19

Phase 2 study (N=117)[10]: 700 mg IV single dose (n=58); placebo (n=59); 28-day follow-up post-dose

Garadacimab + Concomitant hemostasis-impacting treatments

Safety assessment

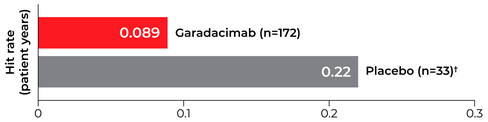
*Investigator-reported AEs may be among the hits identified by the SMQ "hemorrhages"; †Data cut-off: June 16, 2023.
AE, adverse event; HAE, hereditary angioedema; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; q1m, once monthly; SC, subcutaneous; SMQ, Standardized MedDRA Query.

RESULTS

SMQ-identified hits were comparable by study and exposures

HAE clinical study	Number of hits (n)	Median exposure, months	Total exposure, patient years
Phase 2	11 (7)	2.98 (TP1, 12 weeks) 23.9 (TP2, ≥44 week)*	71.89
Pivotal Phase 3 (VANGUARD)	2 (2)	5.98	19.43
Phase 3 OLE	12 (10)	13.80	184.57

Total number of hits: 25 (n=19)



*Total treatment duration; †Patients who received placebo during the placebo-controlled period (TP1) of the Phase 2 study (n=8) and the pivotal Phase 3 study (n=25).[6,7]
OLE, open-label extension; SMQ, Standardized MedDRA Query; TP, Treatment Period.

Medical review identified no garadacimab-related abnormal bleeding events among the SMQ-identified hits for "hemorrhages"

Total number of hits: 25 (n=19)

Medical evaluation of SMQ-identified hits for bleeding events (n=21; number of hits by PT)

- Contusion (10, n=8)
- Traumatic hematoma (3, n=2)
- Hematuria (2, n=1)
- Epistaxis (2, n=2)*
- Intermenstrual bleeding (1)
- Occult blood in urine (1)
- Vaginal hemorrhage (1)
- Blood extravasation (1)

ISRs, not classified as bleeding events (n=4)†

Garadacimab-related abnormal bleeding events identified: 0

*One SMQ-identified hit was reported as an AESI per protocol by investigators (mild epistaxis, resolved, not related to garadacimab); †ISRs (n=4) detected by SMQ were filtered out as these were classified as ISRs, not as bleeding events, per medical review.
AESI per protocol, adverse event of special interest; ISR, injection-site reaction; PT, preferred term; SMQ, Standardized MedDRA Query.

No abnormal bleeding events were identified upon garadacimab administration with concomitant hemostasis-impacting treatments

Investigator-reported bleeding events	Number of patients with concomitant use of garadacimab and hemostasis-impacting treatments
Phase 2 HAE	
1 **None related to garadacimab** Epistaxis* (n=1), mild, patient recovered	**–** **No record of concomitant hemostasis-impacting treatments†**
Pivotal Phase 3 HAE	
0	**4** **Ongoing therapy:** ticagrelor (n=1), aspirin (n=2), apixaban (n=1)
Phase 3 OLE HAE	
2 **None related to garadacimab** Vaginal hemorrhage (n=1), contusion (bruised right toe, n=1); both occurred within 1–2 months of aspirin administration	**20** **One-off treatments:** aspirin (n=5), enoxaparin (n=2), mucopolysaccharide polysulfuric acid ester (n=1), heparinoid (n=1) **Ongoing therapy:** aspirin (n=8), apixaban (n=2), ticagrelor (n=1)
Phase 2 COVID-19	
7 **None related to garadacimab** • **Placebo group** 4 events (n=1/59), serious and severe‡ • **Garadacimab group** 3 events of epistaxis (n=3/58) • 2 mild and resolved • 1 severe and not resolved	**55** **Received concomitant hemostasis-impacting treatments at the time of garadacimab infusion or during follow-up** Enoxaparin (n=33), aspirin + enoxaparin (n=10), aspirin + enoxaparin + heparin (n=3), aspirin (n=2), enoxaparin + apixaban (n=2), enoxaparin + heparin + apixaban (n=1), enoxaparin + heparin + apixaban + aspirin (n=1), enoxaparin + heparin + epoprostenol§ (n=1), enoxaparin + rivaroxaban (n=1), heparin (n=1)

*Garadacimab 600 mg SC dosing; †Per-protocol prohibited therapies: any anticoagulant or antiplatelet therapy, including low-dose aspirin taken prophylactically; ‡Hemorrhagic stroke, subarachnoid hemorrhage, thrombocytopenia, and subdural hematoma; §Platelet aggregation inhibitor.
HAE, hereditary angioedema; OLE, open-label extension.

References

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Disclosures

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