Clinical Study Experience Suggests No Impact on Hemostasis Among Patients With Hereditary Angioedema Receiving Garadacimab and Undergoing Surgical/Medical Procedures

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CONCLUSIONS

- **Clinical study data demonstrates that inhibition of activated factor XII (FXIIa) via treatment with garadacimab does not impact hemostasis in patients with hereditary angioedema (HAE) who are concomitantly undergoing surgical/medical procedures**
- **These findings are consistent with observations of an absent bleeding phenotype in individuals with a congenital factor XII deficiency**
- **Additionally, the incidence of investigator-reported HAE attacks triggered by a surgical/medical procedure was low**

BACKGROUND

- Garadacimab (a first-in-class, fully human, anti-FXIIa antibody) has demonstrated durable efficacy against HAE attacks, and a favorable long-term safety profile in Phase 2 and Phase 3 studies[1-3]
- As FXIIa initiates the intrinsic coagulation pathway, abnormal bleeding events were explored as adverse events of special interest (AESIs) per protocol in the Phase 2, Phase 3 (VANGUARD), and long-term Phase 3 open-label extension (OLE) studies[1-4]
- FXII deficiency does not impact hemostasis *in vivo*, and individuals with a congenital FXII deficiency do not have an increased risk of abnormal bleeding.[5,6] Additionally, prior clinical evidence from HAE and COVID-19 studies has demonstrated that garadacimab has no impact on hemostasis[7]
- Since surgical/medical procedures can be associated with bleeding, the potential impact of FXIIa inhibition with garadacimab on hemostasis was explored in patients who underwent these procedures

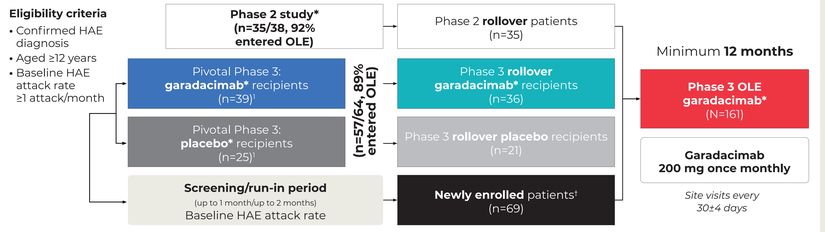
OBJECTIVE

- To explore the potential impact of garadacimab use on hemostasis in patients with HAE undergoing concomitant surgical/medical procedures during the Phase 3 OLE study

STUDY DESIGN

- Data from the ongoing Phase 3 OLE study were analyzed (data cutoff: June 16, 2023)
- Data from patients undergoing concomitant surgical/medical procedures while receiving garadacimab were aggregated and analyzed *post hoc* for any simultaneous abnormal bleeding event
  - Events were analyzed on a case-by-case basis and were based on medical judgement

Phase 3 OLE study design[3]



Primary endpoint (HAE-C1INH)
- TEAEs[§] (N=159)

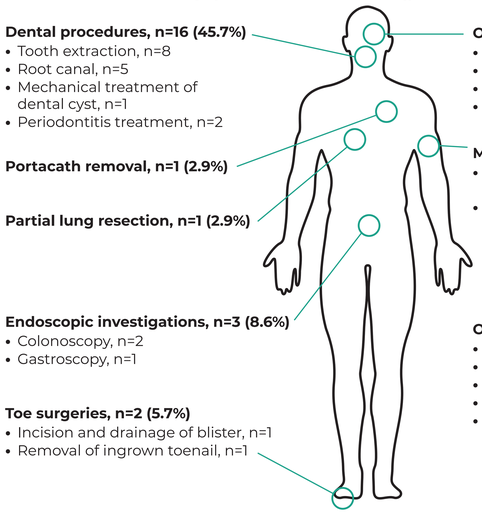
Secondary safety endpoints (HAE-C1INH or HAE-nC1INH)
- SAEs
- TEAEs leading to death
- Related TEAEs
- TEAEs leading to discontinuation
- TEAEs by severity
- ADA
- Laboratory findings reported as AEs
- **AESIs per protocol[¶]**

*Garadacimab was administered once monthly; †Newly enrolled patients received a loading dose of garadacimab (2 × 200 mg) SC as their first dose; ‡Patients may use acute ODT to treat emerging HAE attacks if the medication has previously been shown to be effective; §Including number/percentage of TEAEs, the number/proportion of patients with TEAEs, and TEAE rates per administration of study drug and per patient-year; ¶AESIs per protocol include abnormal bleeding, thromboembolic events, severe hypersensitivity, and anaphylaxis in Phase 3 studies.
ADA, anti-drug antibody; AESI, adverse event of special interest; HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema with C1-inhibitor deficiency or dysfunction; HAE-nC1INH, hereditary angioedema due to normal C1INH; ODT, on-demand treatment; OLE, open-label extension; SAE, serious adverse event; SC, subcutaneous; STP, short-term prophylaxis; TEAE, treatment-emergent adverse event.

RESULTS

Twenty-five of 161 patients underwent a total of 35 concomitant surgical/medical procedures

Number (%) of concomitant surgical/medical procedures



Dental procedures, n=16 (45.7%)
- Tooth extraction, n=8
- Root canal, n=5
- Mechanical treatment of dental cyst, n=1
- Periodontitis treatment, n=2

Portacath removal, n=1 (2.9%)

Partial lung resection, n=1 (2.9%)

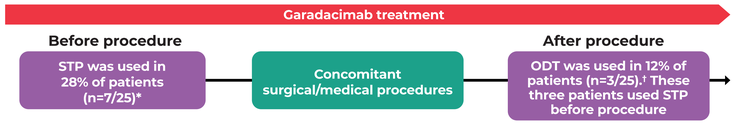
Endoscopic investigations, n=3 (8.6%)
- Colonoscopy, n=2
- Gastroscopy, n=1

Toe surgeries, n=2 (5.7%)
- Incision and drainage of blister, n=1
- Removal of ingrown toenail, n=1

Ophthalmic surgeries, n=5 (14.3%)
- Selective laser trabeculoplasty, n=1
- Bilateral ptosis repair, n=1
- Photorefractive keratectomy, n=1
- Descemet's stripping endothelial keratoplasty, n=2

Muscle repair surgeries, n=2 (5.7%)
- Arthroscopic rotator cuff repair, n=1
- Right biceps tenotomy and repair, n=1

Other, n=5 (14.3%)
- Cutaneous cyst surgery, n=1
- Biopsy, n=1
- Nevus removal, n=1
- Removal of basal cell carcinoma, n=1
- Removal of syringoma, n=1



Most patients (18/25 [72%]) did not receive STP before their procedures or ODT after their procedures

*STP was used on nine occasions prior to 10/35 procedures (29%): one patient received STP with one therapy prior to two separate procedures that occurred on the same day, one patient received both Berinert 1000 IU and 500 IU IV prior to a single procedure, and one patient had two separate procedures for which they used an STP each time. Therapies used for STP were Berinert 500 IU IV: 3/9 (33%); Berinert 1000 IU IV: 3/9 (33%); Berinert 3000 IU IV: 2/9 (22%); Cinryze 1000 IU IV: 2/9 (22%); †ODT was used on three occasions following 4/35 procedures (11%); one patient received ODT following two separate procedures that occurred on the same day. ODTs used were Berinert 1000 IU IV: 1/3 (33%); Berinert 3000 IU IV: 1/3 (33%); Icatibant 30 mg SC: 1/3 (33%).
IU, international unit; IV, intravenous; ODT, on-demand treatment; SC, subcutaneous; STP, short-term prophylaxis.

Garadacimab treatment (median exposure 17.6 months) did not impact hemostasis in patients with HAE undergoing concomitant surgical/medical procedures

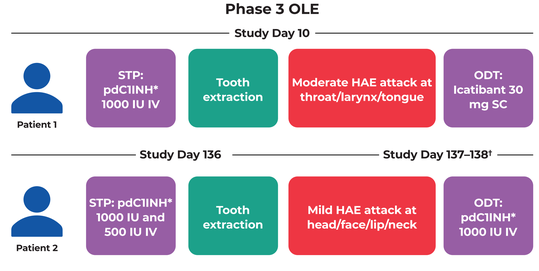
Number (%) of TEAEs following the 35 surgical/medical procedures	
Any TEAE	9 (25.7)
AESI per protocol*	0 (0)
Abnormal bleeding	**0 (0)**

All TEAEs† were of mild/moderate intensity, unrelated to garadacimab, and completely resolved

No abnormal bleeding events were reported

*AESIs per protocol included abnormal bleeding, thromboembolic events, severe hypersensitivity, and anaphylaxis in Phase 3 studies; †Gravitational edema (n=1), throat irritation (n=1), pain following tooth extraction (n=2), hypersensitivity reaction to amoxicillin (n=1), post-procedural fever (n=1), post-operative pain (n=1), surgical wound complications (n=1), wound complication/pain following removal of portacath (n=1).
AESI, adverse event of special interest; HAE, hereditary angioedema; TEAE, treatment-emergent adverse event.

The incidence of investigator-reported HAE attacks following concomitant surgical/medical procedures was low, occurring in 2/25 patients



No investigator-reported HAE attacks occurred among any of the other 23 patients following concomitant surgical/medical procedures, including among patients who did not receive STP (n=18)‡

*Berinert; †The HAE attack started on Day 137 and continued until Day 138; ODT was provided on Day 137; ‡Guidelines state that STP is indicated when patients are at increased risk of having an attack due to known triggers such as surgical/medical procedures.[8]
HAE, hereditary angioedema; IU, international unit; IV, intravenous; ODT, on-demand treatment; OLE, open-label extension; pdC1INH, plasma-derived C1-esterase inhibitor; SC, subcutaneous; STP, short-term prophylaxis.

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DISCLOSURES:
This study was funded by CSL Behring LLC. Medical writing support was provided by Arezou Hossein, MPharm, of Helix, OPEN Health Communications, and funded by CSL Behring, in accordance with Good Publication Practice guidelines (GPP 2022).

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