Low Incidence of Garadacimab Immunogenicity With No Impact on Efficacy, Safety, or Pharmacokinetics: Integrated Analysis

Paul K. Keith[1], Anthony Roberts[2], Fiona Glassman[3], Harsha Shetty[3], John-Philip Lawo[4], Lolis Wieman[3], Iris Jacobs[3], Donald S Levy[5]

[1]McMaster University Medical Centre, Hamilton, ON, Canada; [2]CSL Innovation Pty Ltd, Parkville, Victoria, Australia; [3]CSL Behring, King of Prussia, PA, USA; [4]CSL Innovation GmbH, Marburg, Germany; [5]University of California, Irvine, CA, USA.

CONCLUSIONS

- **The incidence rate of garadacimab immunogenicity and anti-drug antibody (ADA) reciprocal titers were low throughout the garadacimab clinical program in hereditary angioedema (HAE)**
- **The presence of treatment-emergent ADAs did not impact pharmacokinetics (PK) and safety**
- **Monthly HAE attack rate was low in patients who developed treatment-emergent ADAs (2.9%), consistent with the attack rate observed in the overall population**

BACKGROUND

HAE[1-3]

- Causes recurrent, unpredictable, debilitating, potentially life-threatening attacks of swelling
- Results from increased levels of bradykinin, a key mediator of HAE attacks

Garadacimab[1,4-10]

- First-in-class, fully human monoclonal antibody (mAb) targeting activated factor XIIa, the principal initiator of the kallikrein–kinin system
- Fully human, high affinity/potency/specificity; decreases bradykinin production *in vitro*
- Garadacimab was evaluated in two Phase 1 single ascending dose studies; a Phase 1, open-label, parallel-group study; a two-part Phase 2 study; a 6-month, placebo-controlled, pivotal Phase 3 (VANGUARD) study, and an ongoing Phase 3 open-label extension (OLE) study (NCT04739059)

Immunogenicity

- Treatment with mAbs may induce ADAs, which may impact PK, efficacy, and safety[11]
- As a novel mAb, immunogenicity of garadacimab was evaluated

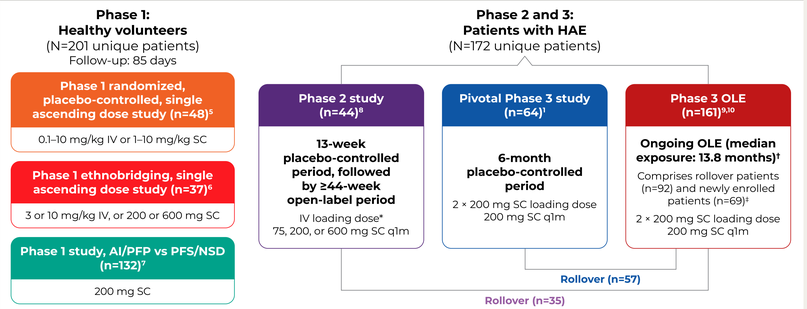
OBJECTIVE

- To report integrated garadacimab immunogenicity data across three Phase 1 studies (healthy volunteers) and in a Phase 2, a pivotal Phase 3 (VANGUARD), and an ongoing Phase 3 OLE study (patients with HAE, data cutoff February 13, 2023)

CLINICAL STUDIES FOR IMMUNOGENICITY ANALYSIS

- Across the clinical development program (**Figure 1**), ADAs against garadacimab were monitored using a bridging immunogenicity assay

Figure 1. Integrated immunogenicity analysis



*IV loading doses of either placebo or garadacimab 40, 100, or 300 mg, followed by either placebo or garadacimab 75, 200, or 600 mg SC, respectively. Six patients received no loading dose; †Data cutoff: February 2023; ‡Newly enrolled patients received one 400 mg SC loading dose as their first dose.
AI/PFP, autoinjector/prefilled pen; HAE, hereditary angioedema; IV, intravenous; OLE, open-label extension; PFS/NSD, prefilled syringe with needle safety device; q1m, once monthly; SC, subcutaneous.

RESULTS

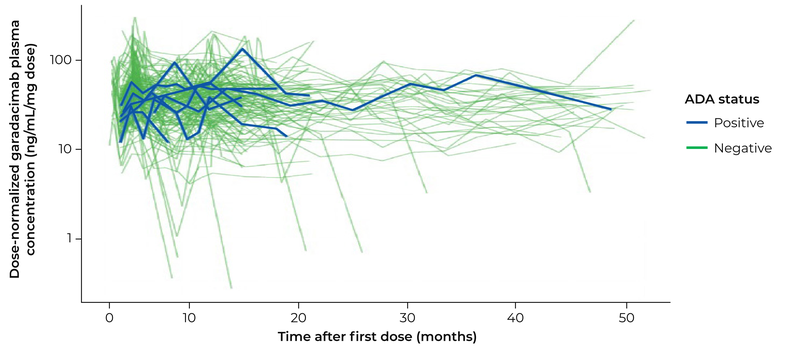
- No ADAs were reported following a single dose in healthy volunteers (N=201) during any of the three Phase 1 studies
- Of 172 unique patients who participated in the Phase 2, pivotal Phase 3, and Phase 3 OLE studies, five patients (2.9%) developed ADAs against garadacimab, all with low reciprocal titers (≤320), regardless of treatment exposure (**Table 1**)

Table 1. Summary of immunogenicity data

Patient	Study	Exposure to garadacimab, months	ADA reciprocal titer	Treatment month
1*	Pivotal Phase 3	5.9	10	≈5.9
	Phase 3 OLE	6.8	160	6
2	Phase 3 OLE	14.3	10	12
3		5.3	320	End of treatment†
4		13.7	10	12
5		13.5	10	12

The titers were categorized as "low" based on the particular assay used and factoring in the sensitivity, assay cutpoint, and the dilution scheme applied. A titer of 320 meant that a signal was not detected after 5 doubling dilutions; the minimum required dilution of the assay was 10.
*Patient rolled over from the pivotal Phase 3 (VANGUARD) study to the OLE study and had treatment-emergent ADAs in both studies; †Patient discontinued garadacimab treatment in the Phase 3 OLE following a moderate ISR (abdomen irritation at injection site, discontinued at Month 6), which recovered/resolved.
ADA, anti-drug antibody; OLE, open-label extension.

Figure 2. Similar dose-normalized garadacimab plasma concentrations observed in patients with ADAs (positive) compared with patients without ADAs (negative)



In lieu of a suitably sensitive neutralizing antibody assay to detect the presence of neutralizing antibodies in ADA-positive patients, an alternative approach to characterize clinically-meaningful neutralizing ADA activity using an integrated clinical dataset to evaluate ADA data with garadacimab exposure, efficacy, PK/PD activity, and safety was undertaken.
The garadacimab concentration–time profile includes the five patients with treatment-emergent ADAs plus two additional patients who had ADAs prior to garadacimab treatment.
The green line approaching 0 ng/mL/mg dose represents patients completing treatment.
ADA, anti-drug antibody; PD, pharmacodynamics; PK, pharmacokinetics.

- All reported treatment-emergent adverse events (**Table 2**) in patients with treatment-emergent ADAs resolved and were mild or moderate in severity and were not associated with ADAs

Table 2. Safety in patients with HAE with treatment-emergent ADAs

Patient	Study	TEAEs unrelated to garadacimab	TEAEs related to garadacimab
1*	Pivotal Phase 3 and OLE	None	None
2	Phase 3 OLE	• URTI • Increased blood creatinine level • COVID-19	None
3†‡		• Headache • Dysmenorrhea • Muscle contracture • Back pain • Depression • Anxiety • Insomnia • Pain • Abdominal pain • GI disorder	• Erythema • Headache • Injection-site erythema • Injection-site irritation
4		None	None
5		• Myalgia • Pyrexia	• Injection-site erythema • Injection-site pruritus

*Patient rolled over from the pivotal Phase 3 (VANGUARD) study to the OLE study and had treatment-emergent ADAs in both studies; †Patient discontinued garadacimab treatment in the Phase 3 OLE following a moderate ISR (abdomen irritation at injection site, discontinued at Month 6), which recovered/resolved; ‡Patient also had a history of fibromyalgia, complicating differentiation between TEAEs and the symptoms of fibromyalgia.
ADA, anti-drug antibody; GI, gastrointestinal; HAE, hereditary angioedema; ISR, injection site reaction; OLE, open-label extension; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

- Monthly HAE attack rate in the presence of ADAs during garadacimab treatment ranged from 0 (attack-free) to 0.2 (**Table 3**)
  - Consistent with pivotal Phase 3 (mean 0.27 vs 3.07 during run-in)[1] and Phase 3 OLE (mean 0.16 vs 3.57 during run-in)[10] studies

Table 3. Monthly HAE attack rate in patients with HAE with treatment-emergent ADAs

Patient	Study	Monthly HAE attack rate during run-in†	Monthly HAE attack rate during treatment period
1*	Pivotal Phase 3	1.2	0
	Phase 3 OLE	1.2	0
2	Phase 3 OLE	5.2	0.2
3		1.7	0
4		2.0	0
5		1.3	0

*Patient rolled over from the pivotal Phase 3 (VANGUARD) study to the OLE study and had treatment-emergent ADAs in both studies; †In the pivotal Phase 3 (VANGUARD) study, the run-in period was 1–2 months, in order to confirm disease activity and baseline number of HAE attacks per month. In the Phase 3 OLE, the run-in period was 1–2 months, in order to confirm newly enrolled patients' underlying disease statuses and to assess their eligibility for enrollment.
ADA, anti-drug antibody; HAE, hereditary angioedema; OLE, open-label extension.

References

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Disclosures

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