A Phase 1, Randomized, Open-Label, Parallel-Group Study Comparing Pharmacokinetic Properties of Garadacimab Administered by Subcutaneous Pre-filled Syringe Assembled to Autoinjector/Pre-filled Pen versus Pre-filled Syringe Assembled to Needle Safety Device in Healthy Adults

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CONCLUSIONS

- **Pharmacokinetic (PK) properties were comparable following a single subcutaneous (SC) dose of garadacimab 200 mg when administered via an autoinjector/pre-filled pen (AI/PFP) or a pre-filled syringe/needle safety device (PFS/NSD)**
- **Exposures were similar for injection sites (abdomen, thigh, and upper arm) and devices (AI/PFP and PFS/NSD)**
- **Administration via AI/PFP and NSD had favorable safety and tolerability profiles**

BACKGROUND

Hereditary angioedema (HAE)[1,2]

- Rare genetic disorder that causes recurrent, unpredictable, debilitating, and potentially life-threatening attacks
- Dysregulation of the kallikrein–kinin pathway leads to uncontrolled production of bradykinin, the key mediator of HAE attacks
- Activated factor XII (FXIIa) is the principal initiator of the contact system, which is responsible for regulating the kallikrein–kinin pathway and, ultimately, bradykinin production

Garadacimab[3,4]

- First-in-class, fully human immunoglobulin G4 monoclonal antibody targeting FXIIa for the prophylaxis of HAE attacks
- High affinity, potency, and specificity for FXIIa, shown to decrease bradykinin production
- In the 6-month pivotal Phase 3 (VANGUARD) study, garadacimab significantly reduced the monthly number of attacks, vs placebo (mean: 0.27 vs 2.01, 87% reduction, respectively; P<0.0001), with a favorable safety and tolerability profile
- Garadacimab can be administered subcutaneously by a pre-filled syringe assembled to either an AI/PFP or a PFS/NSD

Unmet need[5]

- New treatment options with improved efficacy/safety profiles, sustained protection against HAE attacks and convenient administration may help reduce disease and treatment burden for patients

Rationale[6–9]

- Evidence suggests that use of AI/PFP may improve convenience, treatment acceptance, tolerability, and potentially reduce risk of error vs PFS/NSD
- AI/PFP may also alleviate the quality of life impairment associated with additional burden due to chronic treatment of HAE

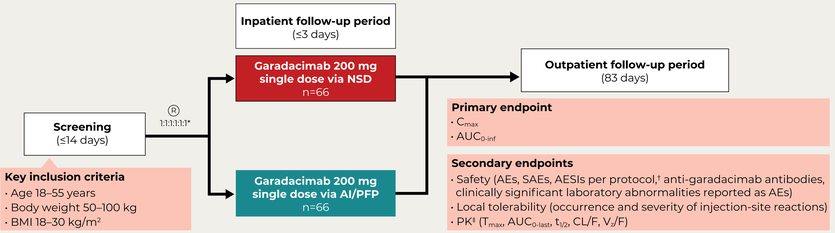
OBJECTIVES

- To characterize and compare the PK properties of a single SC dose of garadacimab 200 mg administered via AI/PFP or PFS/NSD in healthy adults
- To investigate the safety and tolerability of garadacimab administered via AI/PFP or PFS/NSD

References

1. Busse PJ et al. *J Allergy Clin Immunol Pract* 2021;9:132–150.e3; 2. Davis AE 3rd. *Transfus Apher Sci* 2003;29:195–203; 3. Craig TJ et al. *Lancet* 2023;401:1079–1090; 4. Cao H et al. *J Allergy Clin Immunol* 2018;142:1355–1358; 5. Fijen LM et al. *Clin Rev Allergy Immunol* 2021;61:66–76; 6. Berteau C et al. *Patient Prefer Adherence* 2010;4:379–388; 7. Muraro A et al. *Allergy* 2022;77:357–377; 8. Antalfy A et al. *Adv Ther* 2023; 40:4758–4776; 9. Dashiell-Aje E et al. *Patient* 2018;11:119–129.

STUDY DESIGN



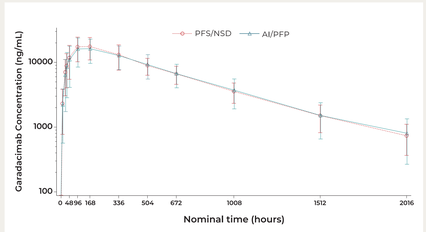
*Subjects randomized to three administration site locations by device as follows: Garadacimab 200 mg single dose via PFS/NSD (abdomen, n=21; thigh, n=22; upper arm, n=23) and garadacimab 200 mg single dose via AI/PFP (abdomen, n=22; thigh, n=22; upper arm, n=22); †AESIs per protocol were defined as severe hypersensitivity including anaphylaxis; ‡Assessed after a single SC injection of garadacimab 200 mg via AI/PFP or PFS/NSD.

Eligible patients were stratified by body weight (<80 kg or ≥80 kg) before randomization. Patients could withdraw from the study at any time at their own request, or at the investigator's or CSL Behring's discretion for safety, behavioral, or administrative reasons (e.g., because of an AE, protocol deviation, loss to follow-up, patient non-compliance, study termination). If a patient was withdrawn from the study, the End of Study Visit 9 assessments were completed and recorded unless the patient withdrew consent.

AE, adverse event; AESI, adverse event of special interest; AI/PFP, autoinjector/pre-filled pen; $AUC_{0\text{-}inf}$, area under the curve from time 0 extrapolated to infinite time; $AUC_{0\text{-}last}$, area under the curve from time 0 to the last measurable concentration; BMI, body mass index; CL/F, apparent clearance; C_{max}, maximum plasma concentration; PFS/NSD, pre-filled syringe/needle safety device; PK, pharmacokinetics; R, randomization; SAE, serious adverse event; $t_{½}$, half-life; T_{max}, time to reach maximum plasma concentration; V_z/F, apparent volume of distribution.

RESULTS

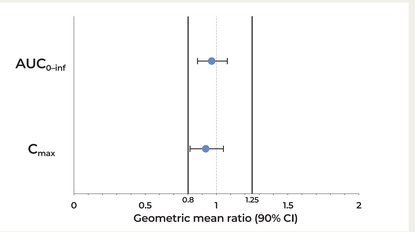
Garadacimab plasma concentration peaks (T_{max}) occurred at a similar time post-dose for AI/PFP and PFS/NSD groups



Error bars represent SD.

- Mean plasma concentration of garadacimab was similar for administration by both AI/PFP and by PFS/NSD

Garadacimab exposure after SC administration via AI/PFP or PFS/NSD met bioequivalence criteria



Error bars represent 90% CI.

- Geometric mean ratio (90% CI) comparing AI/PFP and PFS/NSD was 0.92 (0.81–1.05) for C_{max} and 0.96 (0.87–1.07) for $AUC_{0\text{-}inf}$
- Both 90% CIs encompassed 1.00 and were within the common bioequivalence limits (0.8–1.25)

AI/PFP, autoinjector/pre-filled pen; $AUC_{0\text{-}inf}$, area under the curve from time 0 extrapolated to infinite time; CI, confidence interval; C_{max}, maximum plasma concentration; PFS/NSD, pre-filled syringe/needle safety device; PK, pharmacokinetics; SC, subcutaneous; SD, standard deviation; T_{max}, time to reach maximum plasma concentration.

Disclosures

This study was sponsored by CSL Behring. Writing support provided by OPEN Health Scientific Communications funded by CSL Behring.

RESULTS CONTINUED

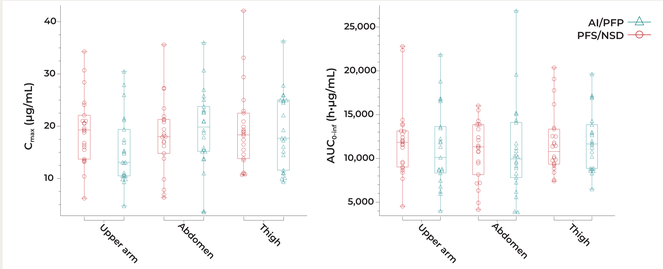
PK properties were consistent with both AI/PFP and PFS/NSD administration

PK parameters	Garadacimab 200 mg PFS/NSD (n=66)	Garadacimab 200 mg AI/PFP (n=66)*	Total (N=132)
C_{max} (µg/mL), mean (SD)	18.9 (7.1)	17.9 (7.4)	18.4 (7.2)
$AUC_{0\text{-}inf}$ (h·µg/mL), mean (SD)	11,542.1 (3723.2)	11,393.5 (4484.7)	11,468.4 (4103.5)
T_{max} (h), median	144.9	145.1	144.9
$AUC_{0\text{-}last}$ (h·µg/mL), mean (SD)	11,066.6 (3514.0)	10,732.8 (4329.3)	10,899.7 (3931.3)
$t_{½}$ (h), mean (SD)	422.5 (69.5)	414.3 (81.1)	418.4 (75.3)
CL/F (L/h), mean (SD)	0.019 (0.007)	0.021 (0.009)	0.020 (0.008)
V_z/F (L), mean (SD)	11.6 (4.2)	12.1 (6.0)	11.8 (5.2)

*65/66 evaluable patients for $AUC_{0\text{-}inf}$, $t_{½}$, CL/F, and V_z/F following loss to follow-up resulting in discontinuation.

AI/PFP, autoinjector/pre-filled pen; $AUC_{0\text{-}inf}$, area under the curve from time 0 extrapolated to infinite time; $AUC_{0\text{-}last}$, area under the curve from time 0 to the last measurable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; PFS/NSD, pre-filled syringe/needle safety device; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, half-life; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution.

Garadacimab PK were similar across three injection sites



Error bars represent minimum and maximum, boxes represent 1st and 3rd quartiles.

AI/PFP, autoinjector/pre-filled pen; $AUC_{0\text{-}inf}$, area under the curve from time 0 extrapolated to infinite time; C_{max}, maximum concentration; PFS/NSD, pre-filled syringe/needle safety device; PK, pharmacokinetics.

Consistent PK properties with AI/PFP and PFS/NSD when injected into abdomen, thigh, and upper arm, respectively:

C_{max} (mean):

- **AI/PFP:** 19.2, 19.3, and 15.3 µg/mL
- **PFS/NSD:** 18.2, 19.3, and 19.1 µg/mL

$AUC_{0\text{-}inf}$ (mean):

- **AI/PFP:** 10,872.9, 11,982.5, and 11,321.9 h·µg/mL
- **PFS/NSD:** 10,807.8, 11,801.9, and 11,963.9 h·µg/mL

Garadacimab 200 mg administered via AI/PFP or PFS/NSD had a favorable safety and tolerability profile

- No deaths, serious treatment-emergent adverse events (TEAEs), TEAEs leading to study withdrawal, or adverse events of special interest per protocol (severe hypersensitivity including anaphylaxis) were reported for either device
- Overall, the incidence of injection site-related TEAEs was low (16.7%), and all were mild in severity