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Exposure-Response Relationships for Axatilimab, a Humanized Monoclonal Antibody Targeting CSF-1R, in Patients With Chronic Graft-Versus-Host Disease

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Introduction

- Axatilimab is a monoclonal antibody targeting colony-stimulating factor 1 receptor on monocytes and macrophages that are critical for inflammation and fibrosis[1,2]
- In a phase 1/2 study (SNDX-6352-0503 [NCT03604692]) of axatilimab in patients with chronic graft-versus-host disease (cGVHD), the overall response rate (ORR) by Cycle 7 Day 1 was 67% (95% CI, 50%–81%) and axatilimab was generally well tolerated[3]
- In the pivotal randomized phase 2 AGAVE-201 study (NCT04710576), the ORR by Cycle 7 Day 1 with axatilimab ranged from 50% to 74% across 3 dose cohorts, with no unexpected safety concerns[4]
- In a previous population pharmacokinetic/pharmacodynamic (PK/PD) analysis, body weight was identified as the only covariate that was associated with >20% change in axatilimab exposure

Objective

- To characterize the exposure-efficacy and exposure-safety relationships for axatilimab among patients with cGVHD after ≥2 prior lines of systemic therapy

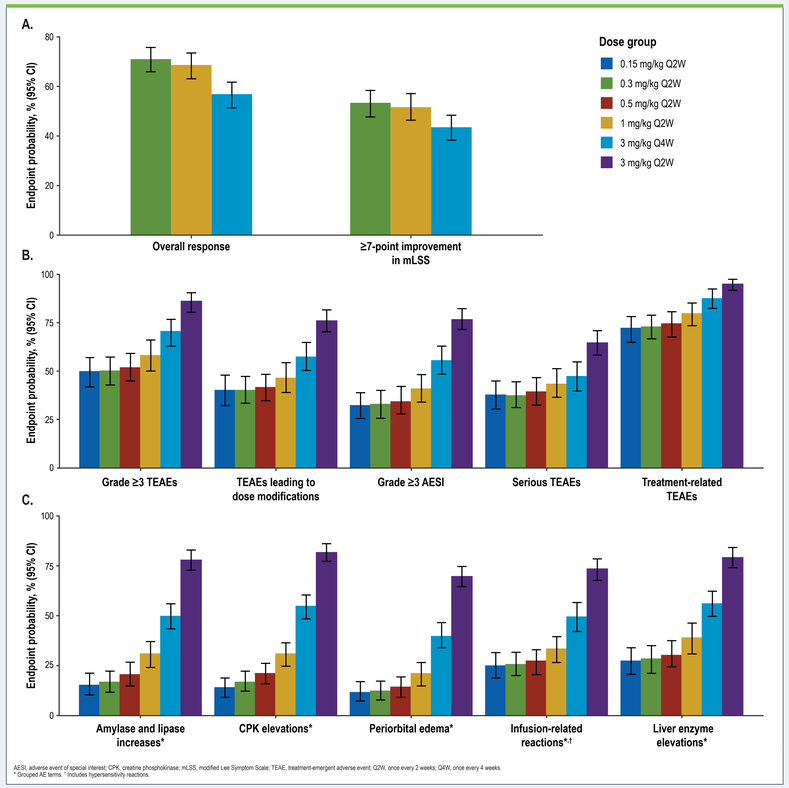
Methods

- Axatilimab exposure metrics were derived from a previously developed population PK/PD model
- The exposure-efficacy relationship was assessed for 2 binary endpoints and 1 time-to-event endpoint in 239 patients from the AGAVE-201 study, and the exposure-safety relationship was assessed for 11 binary endpoints in 278 patients from the AGAVE-201 and SNDX-6352-0503 studies
  - Logistic regression or Cox regression analyses were used for binary or time-to-event endpoints, respectively
- Binary efficacy assessments included overall response and ≥7-point improvement in modified Lee Symptom Scale (mLSS); duration of response, a time-to-event endpoint, was assessed among all patients in AGAVE-201 who achieved an overall response
- Evaluated safety endpoints included 5 general safety assessments (grade ≥3 treatment-emergent adverse events [TEAEs], TEAEs leading to dose modifications, serious TEAEs, treatment-related TEAEs, AEs of special interest) and 6 sets of grouped AE terms (amylase and lipase increases, creatine phosphokinase elevations, liver enzyme elevations, periorbital edema, infections of unspecified etiology [infections not otherwise specified as bacterial, viral, or fungal], and infusion-related reactions)
- To evaluate the effects of body weight with the 0.3 mg/kg once every 2 weeks (Q2W) regimen, exposure-response models were used to predict the effects of body weight on efficacy and safety outcomes that were associated with axatilimab exposure
  - Percentiles of an observed body weight distribution (range, 18.1–151 kg) were used in forward simulations

Results

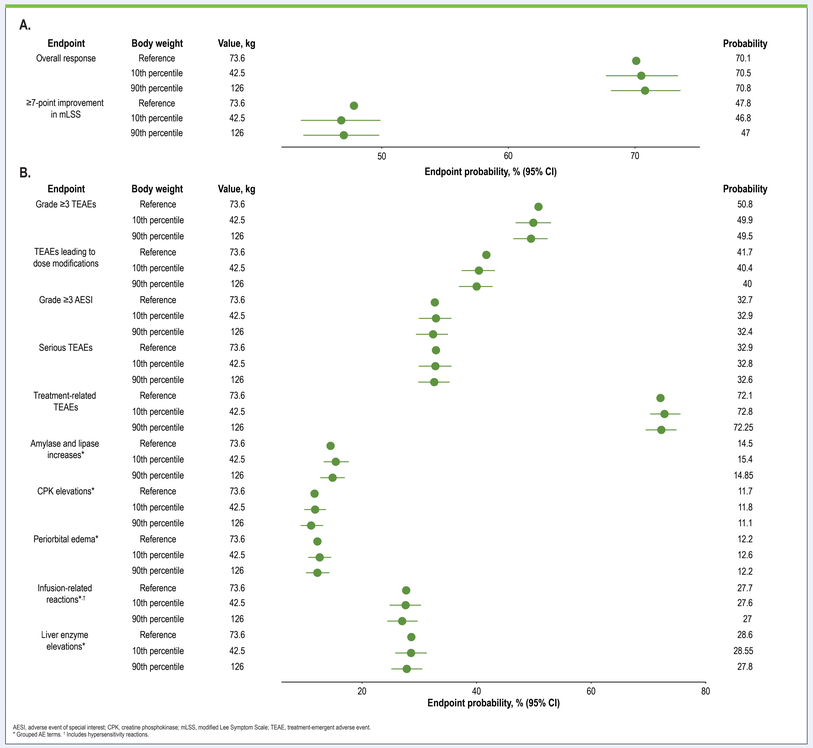
- Overall response and ≥7-point improvement in mLSS were associated with axatilimab exposure, with lower axatilimab exposure (area under the curve after single dose from time 0 to infinity) increasing the probability of response (**Figure 1A**)
- Among the 153 patients with a response, duration of response did not have a significant association with axatilimab exposure (data not shown)
- All safety endpoints except infections of unspecified etiology were associated with axatilimab exposure (area under the curve at steady state), with higher axatilimab exposure increasing the probability of TEAEs (**Figure 1B–C**)
- In forward simulations evaluating the effect of body weight on the axatilimab 0.3 mg/kg Q2W regimen, the maximum differences in median predicted probabilities between the 10th and 90th percentiles with body weight were <1.4% and <1.7% for efficacy and safety, respectively (**Figure 2**)

Figure 1. Model-Predicted Event Rates of Evaluated Dose Levels for (A) Efficacy Endpoints, (B) General TEAE Endpoints, and (C) Additional Safety Endpoints



AESI, adverse event of special interest; CPK, creatine phosphokinase; mLSS, modified Lee Symptom Scale; TEAE, treatment-emergent adverse event; Q2W, once every 2 weeks; Q4W, once every 4 weeks.
* Grouped AE terms. † Includes hypersensitivity reactions.

Figure 2. Model-Predicted Event Rates at 0.3 mg/kg by Body Weight for (A) Efficacy and (B) Safety Endpoints



AESI, adverse event of special interest; CPK, creatine phosphokinase; mLSS, modified Lee Symptom Scale; TEAE, treatment-emergent adverse event.
* Grouped AE terms. † Includes hypersensitivity reactions.

Conclusions

- **These findings support the benefit-risk profile of axatilimab 0.3 mg/kg Q2W in patients with cGVHD**

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