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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 WKDWDUHFULWLFDOIRULQÀPPDWLRQDQG FURVV
- 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, ERGZHLKWZDVLGHQWLÀHGDVWKHRQO\ covariate that was associated with >20% change in axatilimab exposure

Objective

- RFKDDFWL[SRVXUH
  and exposure-safety relationships for axatilimab among patients with cGVHD DIWHUSULRUOLQHVRIVVWHPLFWKHUDS\

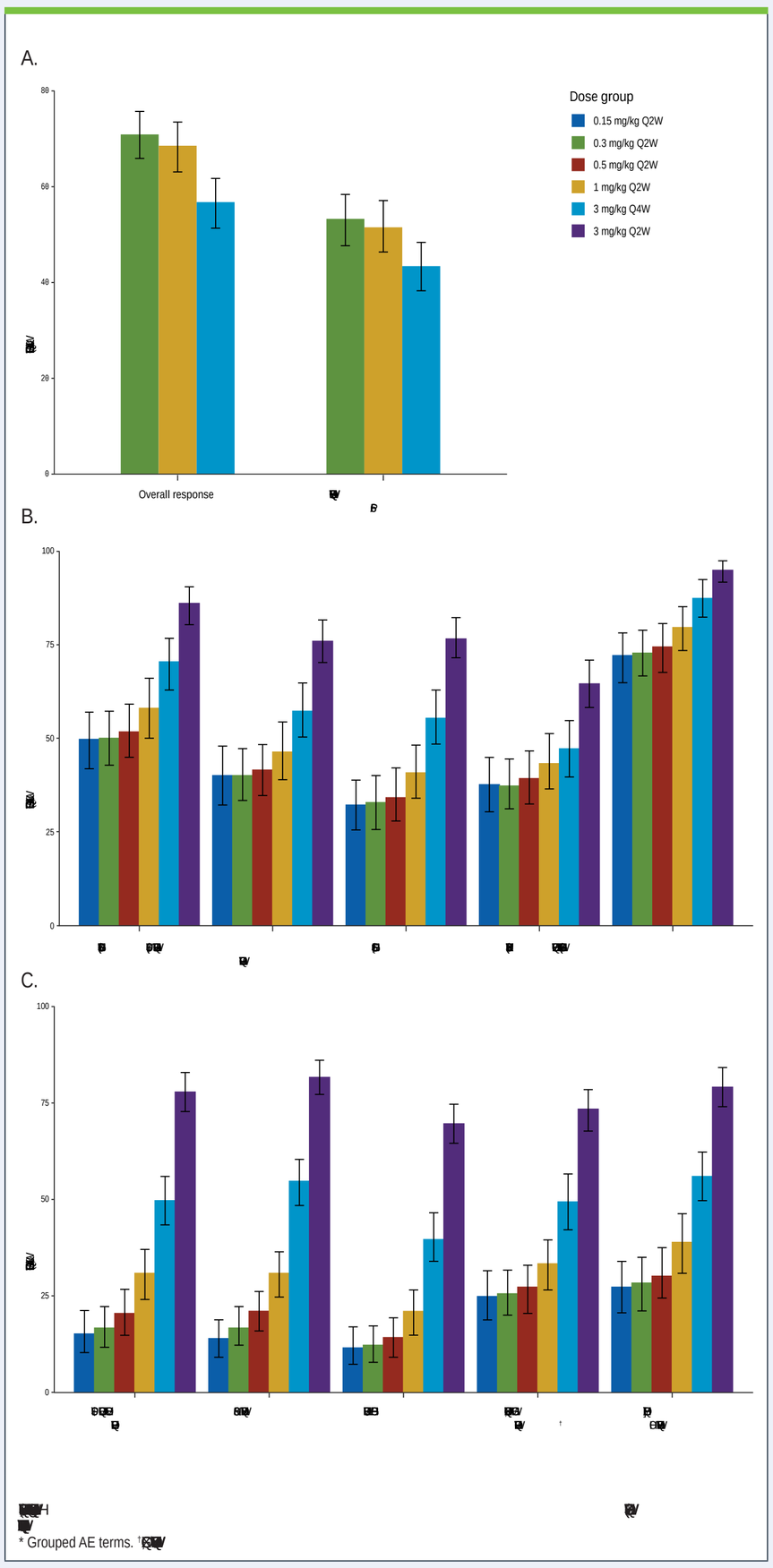
Methods

- Axatilimab exposure metrics were derived from a previously developed population PK/PD model
- 7KHH[SRVXUHHFDFUHODWLRQVKLS 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
  - A detailed explanation of the exposure-response analysis methodology is included in the **Supplemental Methods**
- Exposure-response models were used WRSUHGLFWWKHHIFWVRIERGZHLKWRQ HFDFDQGVDIHWRXWFRPHV

Results

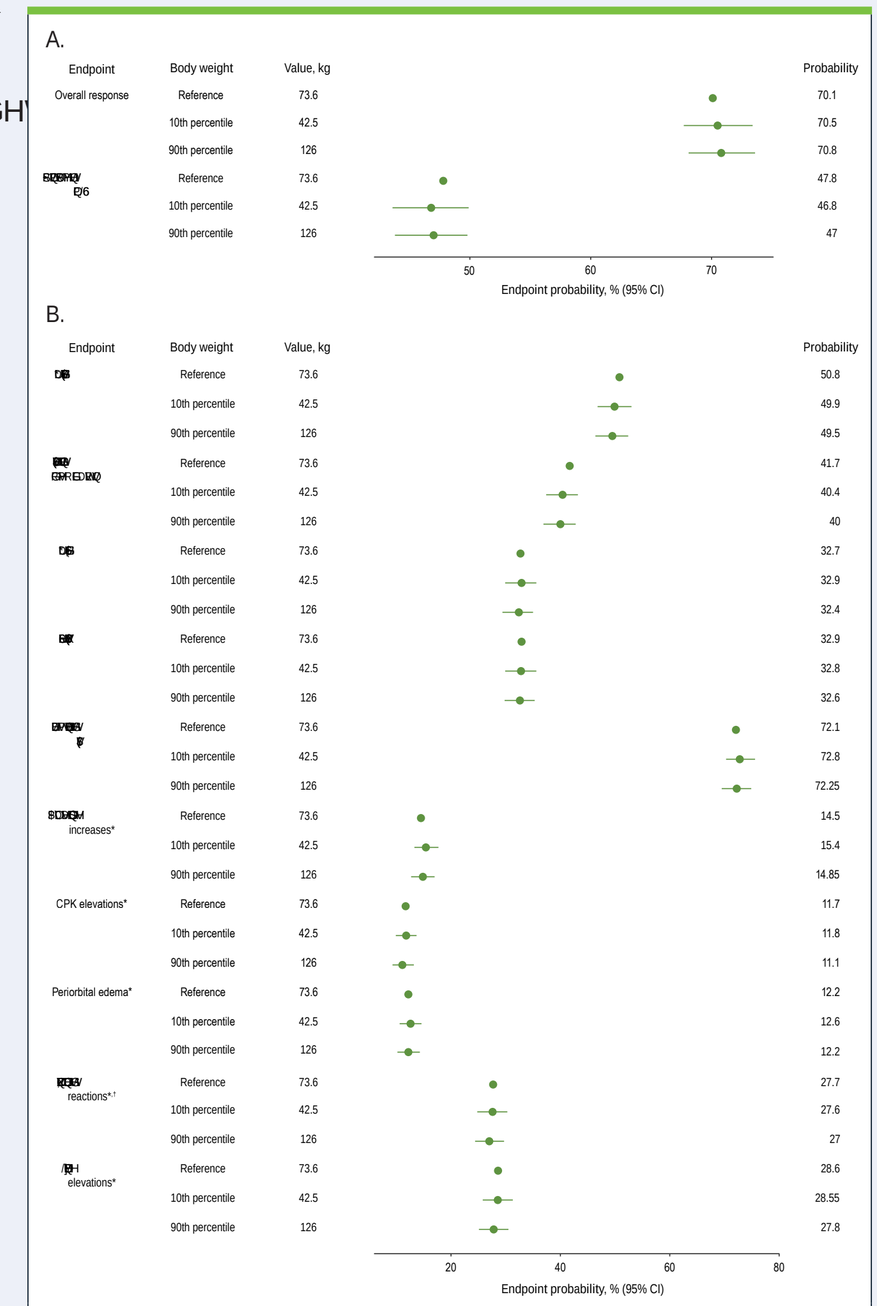
- 2YHUDOOVRQHGLQPSEYHQ Symptom Scale were associated with axatilimab exposure, with lower axatilimab exposure (area under the curve after VLQGOHGRVHIURPWLPHWRQQLWLQFUHDVLQJWKHSUREDELOLW\ of response (**Figure 1A**)
- Among the 153 patients with a response, duration of UHVSRQVHGLGQRWKDYHDQLQÁXHQFHDQGVVRFLDWLRQZLWK axatilimab exposure (data not shown)
- $OOVDIHWHQGSRLQWVH[FHSWLQIHFWLRQVRIXQVSHFLÀHGH were associated with axatilimab exposure (area under the curve at steady state), with higher axatilimab exposure increasing the probability of treatment-emergent adverse events (**Figure 1B–C**)

Figure 1. Model-Predicted Event Rates of Evaluated Dose /



- ,QIRUZDUGVLPXODWLRQVHYOXDWLQJWKHHIFWRIERGZH on the axatilimab 0.3 mg/kg once every 2 weeks (Q2W) UHLPHQWKHPD[LPXPGLHUHQFHVLQPHGLDQSUHGLFWHG probabilities between the 10th and 90th percentiles with ERGZHLKWZHUHDQGIRUHFDFDQGVDIHW\ respectively (**Figure 2**)

Figure 2. Model-Predicted Event Rates at 0.3 mg/kg by Body



Conclusions

YY, XL, JS, and XC are employees and shareholders of Incyte Corporation. AV, VS, CL, and YK are employees of M&S Decisions FZ LLC, a modeling consultancy contracted by Incyte Corporation.

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Supplemental Methods

Exposure-Efficacy and Exposure-Safety Relationships

- Exposure-efficacy relationships were assessed in patients treated in the phase 2 AGAVE-201 study (n=239; axatilimab 0.3 mg/kg once every 2 weeks [Q2W], 1.0 mg/kg Q2W, and 3.0 mg/kg once every 4 weeks [Q4W])
- Binary efficacy assessments included overall response and ≥7-point improvement in modified Lee Symptom Scale; duration of response, a time-to-event endpoint, was assessed among all patients in AGAVE-201 who achieved an overall response
- Exposure-safety relationships were assessed in all treated patients with chronic graft versus host disease (n=278 in AGAVE-201 and SNDX-6352-0503 [axatilimab 0.15 mg/kg Q2W, 0.5 mg/kg Q2W, 1.0 mg/kg Q2W, 3.0 mg/kg Q2W, and 3.0 mg/kg Q4W])
- 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)
- For binary or time-to-event endpoints, logistic or Cox regression analyses, respectively, were performed using predicted axatilimab exposure metrics that were derived from a previously developed population pharmacokinetic/pharmacodynamic (PK/PD) model

Forward Simulations

- To evaluate the effects of body weight with the 0.3 mg/kg Q2W regimen (a covariate identified as potentially significant in the population PK/PD model), forward simulations were completed using percentiles of an observed body weight distribution (range, 18.1–151 kg) for each efficacy and safety outcome that was associated with axatilimab exposure