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Trial in Progress: A Randomized, Open-Label, Phase 3 Study of Axatilimab vs Best Available Therapy in Patients With Chronic Graft-Versus-Host Disease After ≥2 Prior Lines of Systemic Therapy

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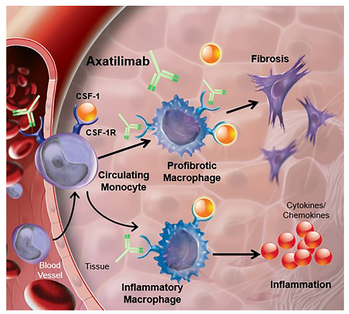
Introduction

- Chronic graft-versus-host disease (cGVHD) is a major cause of morbidity and nonrelapse mortality among patients who undergo allogeneic hematopoietic stem cell transplantation[1]
- In patients with cGVHD, colony-stimulating factor 1 receptor (CSF-1R) dependent monocytes and macrophages contribute to tissue inflammation and fibrosis, which can lead to multiorgan damage[2-5]
- Treatment with axatilimab, a high-affinity anti–CSF-1R monoclonal antibody, preferentially depletes nonclassical monocytes from circulation and reduces the density of CSF-1R+ macrophages in affected tissues[6] (**Figure 1**)

Figure 1. Axatilimab Mechanism of Action



CSF-1, colony-stimulating factor 1; CSF-1R, colony-stimulating factor 1 receptor.

- AGAVE-201, a phase 2, pivotal, randomized, open-label study, evaluated axatilimab at doses of 0.3 mg/kg every 2 weeks (Q2W), 1 mg/kg Q2W, and 3 mg/kg every 4 weeks in patients ≥2 years of age with active, refractory, or recurrent cGVHD after ≥2 lines of systemic therapy[7]
  - Patients in the axatilimab 0.3 mg/kg Q2W cohort achieved an overall response rate (ORR) of 74% in the first 6 treatment cycles, and this dose was generally well tolerated, with 6% of patients experiencing adverse events leading to axatilimab discontinuation[7]
- On the basis of findings from AGAVE-201, axatilimab was approved in the United States in August 2024 for the treatment of cGVHD after failure of ≥2 prior lines of therapy in adult and pediatric patients weighing ≥40 kg[8]

Objective

- This randomized, multicenter, open-label, phase 3 study will evaluate the efficacy and safety of axatilimab 0.3 mg/kg Q2W versus best available therapy (BAT) in patients with cGVHD after ≥2 prior lines of systemic therapy, including corticosteroids and ruxolitinib

Methods

Patients

- The study (NCT06821542; EU CT: 2024-518973-32-00) is currently open and recruiting, and approximately 300 patients in Europe with active moderate to severe cGVHD requiring systemic immune suppression will be enrolled (**Table 1**)

Table 1. Key Eligibility Criteria

Inclusion criteria
• Age ≥12 years
• Active, moderate to severe cGVHD requiring systemic immune suppression*
• At least 2 lines of prior systemic therapy for cGVHD, including corticosteroids and ruxolitinib
• KPS score ≥60 (patients aged ≥16 y) or LPS score ≥60 (patients aged <16 y)
• History of 1 allo-HSCT from any donor type and any graft source
• Patients may have overlap cGVHD and may use concomitant corticosteroids/CNIs/mTOR inhibitors
Exclusion criteria
• aGVHD without manifestations of cGVHD
• Evidence of relapsed hematologic disease or treatment for relapse (including donor lymphocyte infusion)
• Maintenance therapy for primary hematologic disease started within 4 weeks prior to Day 1, or planned for after Day 1
• For approved or commonly used cGVHD treatments (other than corticosteroids, CNIs, and mTOR inhibitors), a washout period of 2 weeks or 5 half-lives is required at study enrollment
• Severe renal impairment, impaired liver function, or active, uncontrolled infection

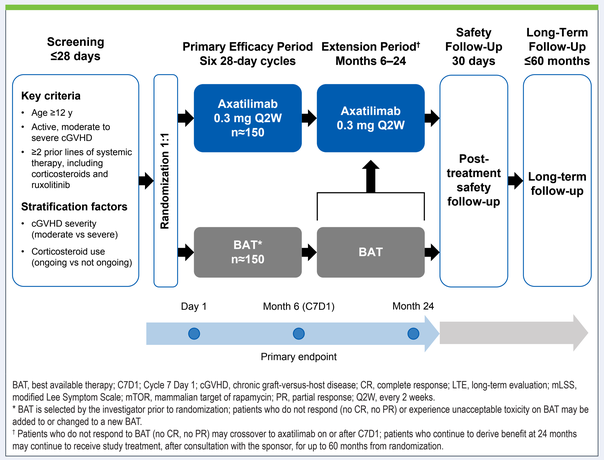
aGVHD, acute graft-versus-host disease; allo-HSCT, allogeneic hematopoietic stem cell transplantation; cGVHD, chronic graft-versus-host disease, CNI, calcineurin inhibitor; KPS, Karnofsky Performance Scale; LPS, Lansky Performance Scale; mTOR, mammalian target of rapamycin.
* Active cGVHD is defined per 2014 NIH Consensus Criteria.[9] Moderate cGVHD is defined as ≥1 organ (except lung) with a score of 2, ≥3 organs with a score of 1, or a lung score of 1. Severe cGVHD is defined as ≥1 organ with a score of 3 or a lung score of 2–3.

- All patients will provide written informed consent before initiating any study-related procedures

Study Design and Treatment

- This is a multicenter, randomized, open-label, phase 3 study evaluating the efficacy and safety of axatilimab compared with BAT in patients with cGVHD after ≥2 lines of systemic therapy (**Figure 2**)
  - Patients will be screened for up to 28 days and randomly assigned in a 1:1 ratio to axatilimab 0.3 mg/kg every 2 weeks (Q2W) or BAT
  - Patients will be treated for a period of up to 24 months (in 28-day cycles) or until initiation of new cGVHD therapy, unacceptable toxicity, relapse of hematologic disease, or withdrawal of consent
  - Patients who continue to derive benefit from study treatment after 24 months may continue for up to 60 months from randomization, after consultation with the study sponsor

Figure 2. Study Design



BAT, best available therapy; C7D1; Cycle 7 Day 1; cGVHD, chronic graft-versus-host disease; CR, complete response; LTE, long-term evaluation; mLSS, modified Lee Symptom Scale; mTOR, mammalian target of rapamycin; PR, partial response; Q2W, every 2 weeks.
* BAT is selected by the investigator prior to randomization; patients who do not respond (no CR, no PR) or experience unacceptable toxicity on BAT may be added to or changed to a new BAT.
† Patients who do not respond to BAT (no CR, no PR) may crossover to axatilimab on or after C7D1; patients who continue to derive benefit at 24 months may continue to receive study treatment, after consultation with the sponsor, for up to 60 months from randomization.

- Patients will be stratified by cGVHD severity at screening (moderate vs severe) and by the use of systemic corticosteroids at randomization (ongoing vs not ongoing)
- Concomitant use of corticosteroids, including topical and inhaled formulations, is permitted; patients receiving systemic corticosteroids must be on a stable dose for ≥2 weeks before the first day of the first treatment cycle
- Concomitant use of a calcineurin inhibitor (CNI) or a mammalian target of rapamycin (mTOR) inhibitor for GVHD prophylaxis, management of acute GVHD, or treatment of cGVHD is permitted if treatment was started ≥2 weeks before the first day of the first treatment cycle
- BAT for each patient is selected by the investigator prior to randomization from among the following: CNI (cyclosporine or tacrolimus), extracorporeal photopheresis, mycophenolate mofetil, mTOR inhibitor (everolimus or sirolimus), rituximab, pentostatin, proteasome inhibitor, imatinib, or ibrutinib
- Patients receiving BAT who do not respond to treatment or experience unacceptable toxicity prior to C7D1 may add or switch to a new BAT, but this will be considered treatment failure
- On or after the C7D1 visit, patients receiving BAT who do not achieve at least PR, have worsening cGVHD symptoms, or experience unacceptable toxicity may cross over to the axatilimab arm

Endpoints and Assessments

- Primary and secondary study endpoints are shown in **Table 2**

Table 2. Study Endpoints

Primary endpoint
• OR at 6 months: CR or PR at 6 months (C7D1) in the absence of new systemic cGVHD therapy*
Key secondary endpoint
• FFS: time from randomization to addition or initiation of another systemic cGVHD therapy, relapse of underlying disease, or death from any cause
Other secondary endpoints
• Symptom response: patients with ≥7-point improvement in mLSS total score (assessed in patients aged ≥18 y)
• OR at 12 months: CR or PR at 12 months in the absence of new systemic cGVHD therapy
• BOR: best response (CR or PR) on or before C7D1 and up to initiation of new cGVHD therapy
• DOR: time from first PR or CR to progression of cGVHD from baseline scoring, new systemic cGVHD therapy, or death from any cause
• Organ-specific response
• OS: time from randomization to death from any cause
• NRM: time from randomization to death not preceded by relapse of primary hematologic disease
• Time from randomization to relapse of primary hematologic disease
• Percent reduction in daily corticosteroid dose at C7D1 and patients successfully tapered off corticosteroids at C7D1
Safety and tolerability
• Safety and tolerability will be assessed by examining the frequency of AEs (including SAEs), including changes in clinical assessments, laboratory assessments, and KPS/LPS scores

AE; adverse event; BOR, best overall response; C7D1, Cycle 7 Day 1; cGVHD, chronic graft-versus-host disease; CR, complete response; DOR, duration of response; FFS, failure-free survival; KPS, Karnofsky Performance Scale; LPS, Lansky Performance Scale; mLSS, modified Lee Symptom Scale; NRM, nonrelapse mortality; OR, objective response; OS, overall survival; PR, partial response; SAE, serious adverse event.
* Response assessment is based on 2014 NIH Consensus Criteria for Clinical Trials in cGVHD and the refined NIH response algorithm for cGVHD in joints and fascia.[10,11]

- Overall cGVHD severity scoring, individual organ scoring, and response evaluation (complete response [CR] or partial response [PR]) will be assessed on Day 1 (D1) of Cycle 1 (baseline; C1D1), D1 and D15 of Cycles 2–3, D1 of Cycles 4–13, and every 12 weeks (Q12W) thereafter, as well as at end of treatment
- Changes in patient-reported symptom activity in patients aged ≥18 years will be evaluated using the modified Lee Symptom Scale on the same schedule as severity and response scoring
- Adverse events (AEs) will be monitored from informed consent until ≥30 days after the last dose of study treatment or start of new cGVHD therapy and graded for severity using Common Terminology Criteria for Adverse Events v5.0; the investigator will assess the relationship between study drug and each AE
  - Karnofsky performance scale and Lansky performance scale assessments (for patients aged ≥16 y and <16 y, respectively) will be conducted on D1 of Cycles 1–13 and Q12W thereafter, as well as at the end of treatment
- Patients who complete study treatment and taper after PR or CR or discontinue for reasons other than cGVHD progression or requirement for new cGVHD therapy will be followed for cGVHD response for up to 24 months (Q4W up to 1 year and Q12W thereafter) until initiation of a new cGVHD therapy, end of study, or death
  - Patients who complete post-treatment cGVHD follow-up will be followed for survival and relapse of hematologic disease Q2W for up to 60 months from randomization

Statistical Analysis

- Efficacy analyses will include all patients randomized to the study treatment
- The safety analysis will include all randomized patients who receive ≥1 dose of the study drug

Conclusions

- **This randomized phase 3 study of approximately 300 patients will provide valuable insight into the efficacy and safety of axatilimab vs BAT in adult and pediatric patients with cGVHD who received ≥2 lines of prior systemic therapy, including corticosteroids and ruxolitinib**
- **It is anticipated that patients will participate from approximately 130 sites located in 16 countries in Europe**

Disclosures

MK served as a speakers' bureau member for Gilead, Pfizer, and Jazz Pharmaceuticals and served as a member of an advisory committee for Sanofi. FB has served on advisory boards and received honoraria for lectures or educational events from Gilead, Kite, and Novartis. AECB, PC, and JP have no disclosures to report. JC received honoraria from Bristol Myers Squibb, Incyte Corporation, Novartis, and Sanofi, received speaker fees from Novartis, and received a research grant from Novartis. TG-D received speaker fees from Incyte, Novartis, and Sanofi. WI received honoraria from Medac Pharma, received speaker fees from Novartis, and served as an advisory board member for Gilead, Novartis, Roche, Sobi, and Synairgen. HS received personal fees from BeiGene, the Belgian Hematological Society (BHS), Incyte, Novartis, MAAT Pharma, Mallinckrodt Pharmaceuticals, and Sanofi, all paid to her institution; received nonfinancial support from AbbVie, the CIBMTR (Center for International Bone Marrow Transplantation Research), the EBMT (European Society for Blood and Marrow Transplantation), Pfizer, and Sanofi; and received support from the UZ Leuven Klinische onderzoeks- en opleidingsraad (KOOR) of the University Hospitals of Leuven, Belgium. EdW and MS are employees of Incyte Biosciences International Sàrl and shareholders of Incyte Corporation. CT is an employee and shareholder of Incyte Corporation. DW received honoraria from Behring, Gilead, Incyte Corporation, Mallinckrodt, Novartis, Sanofi, and Takeda and received research funding from Novartis.

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