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Trial in Progress: A Phase 3 Study of Itacitinib or Placebo in Combination With Corticosteroids as Initial Treatment for Chronic Graft-Versus-Host Disease (GRAVITAS-309)

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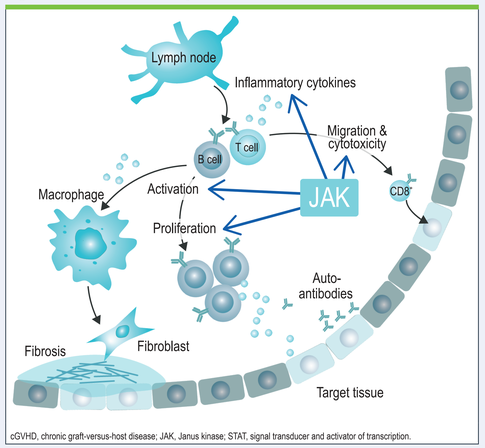
Background

- Chronic graft-versus-host disease (cGVHD) develops in 30%–70% of long-term survivors of hematopoietic cell transplantation (HCT) and is a significant cause of nonrelapse mortality[1,2]
- cGVHD typically manifests with multiorgan pathology (including thymic damage and fibrosis), requires long-term immunosuppression, and significantly impairs physical functioning and overall quality of life (QoL)[1,3]
- Corticosteroids (CS) are the recommended first-line treatment for cGVHD; however, up to 60% of patients treated with CS require additional cGVHD therapy within 2 years[4,5]
- Itacitinib, a potent and selective Janus kinase (JAK)–1 inhibitor, is being investigated for the treatment of patients with acute graft-versus-host disease (aGVHD; NCT03139604) or cGVHD (NCT03584516), as well as in the prophylactic setting (NCT03320642)
  - The JAK/signal transducer and activator of transcription (STAT) pathway is a regulator of immune effector cells and cytokines that potentiate cGVHD **(Figure 1)**[6]

Figure 1. JAK-STAT Pathway in cGVHD



cGVHD, chronic graft-versus-host disease; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

- In murine models, itacitinib improved graft-versus-host disease (GVHD) and survival without affecting engraftment of donor leukocytes[7-9]
- In a phase 1 clinical trial (NCT02614612), itacitinib 200 or 300 mg once daily (QD) was well tolerated in patients with steroid-refractory or treatment-naive aGVHD[10]
  - The overall response rate (ORR) was 75.0% in patients with treatment-naive aGVHD and 70.6% in those with steroid-refractory aGVHD

Objective

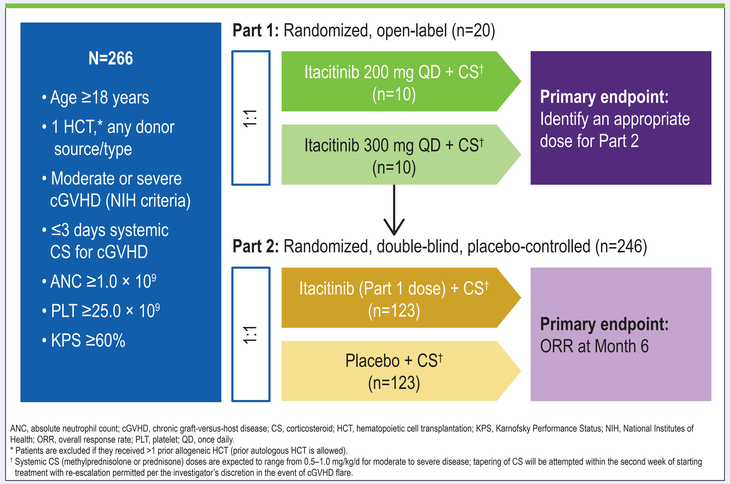
- To summarize the trial design of GRAVITAS-309 (NCT03584516), the first clinical study evaluating the safety and efficacy of itacitinib for the treatment of cGVHD

Methods

Study Design

- GRAVITAS-309 is a 2-part, phase 3 study of itacitinib or placebo in combination with CS as initial treatment for cGVHD **(Figure 2)**

Figure 2. GRAVITAS-309 Study Design



ANC, absolute neutrophil count; cGVHD, chronic graft-versus-host disease; CS, corticosteroid; HCT, hematopoietic cell transplantation; KPS, Karnofsky Performance Status; NIH, National Institutes of Health; ORR, overall response rate; PLT, platelet; QD, once daily.
* Patients are excluded if they received >1 prior allogeneic HCT (prior autologous HCT is allowed).
† Systemic CS (methylprednisolone or prednisone) doses are expected to range from 0.5–1.0 mg/kg/d for moderate to severe disease; tapering of CS will be attempted within the second week of starting treatment with re-escalation permitted per the investigator's discretion in the event of cGVHD flare.

- Part 1: determine an optimal dose of itacitinib (200 mg QD or 300 mg QD) in combination with CS
  - After 20 patients complete 28 days of treatment, an external data monitoring committee will review the data and recommend an appropriate dose for Part 2
- Part 2: evaluate the efficacy and safety of itacitinib in combination with CS using the dose selected in Part 1
  - Approximately 246 patients will be stratified by cGVHD severity and randomized 1:1 to itacitinib plus CS vs placebo plus CS
  - Patients randomized to the placebo group will be allowed to cross over to the itacitinib group after completion of the primary analysis
- Itacitinib treatment will continue until treatment failure, relapse of primary hematologic disease, unacceptable toxicity, or withdrawal of consent, for a maximum of 36 months

Patient Eligibility

- Key inclusion criteria
  - Age ≥18 years
  - Received 1 HCT from any donor type (eg, related or unrelated donor with any degree of human leukocyte antigen matching) and graft source (eg, bone marrow, peripheral blood cells, cord blood) for a hematologic malignancy or disorder
  - Evidence of myeloid and platelet engraftment (absolute neutrophil count ≥1.0 × 10^9/L and platelet count ≥25 × 10^9/L)
  - Active moderate or severe cGVHD per National Institutes of Health Consensus Criteria
    - Patients who transition from active aGVHD to cGVHD without tapering off of CS (<0.25 mg/kg/d) ± calcineurin inhibitors are also eligible
  - Karnofsky Performance Status ≥60%
- Key exclusion criteria
  - Received >1 prior HCT (except autologous)
  - Had >3 days of systemic CS treatment for cGVHD
  - Received any other systemic treatment for cGVHD, including extracorporeal photopheresis
  - Prior and concomitant use of calcineurin inhibitors and topical/inhaled steroids is acceptable
  - Presence of active, uncontrolled infection
  - Prior treatment with a JAK inhibitor within 8 weeks of randomization
    - Patients who previously received a JAK inhibitor for aGVHD are eligible only if they achieved a complete response (CR) or partial response (PR)
  - Maintenance therapy for the primary hematologic disease started within 4 weeks of initiation of study treatment (Day 1) or plans to start maintenance therapy after Day 1

Assessments and Analyses

- Part 1 primary endpoints: dose-limiting toxicities through Day 28 and clinical safety and laboratory assessments **(Table 1)**
  - Key secondary endpoints: pharmacokinetic (PK) parameters and efficacy outcomes
- Part 2 primary endpoint: ORR (proportion of patients with a CR or PR) at 6 months **(Table 1)**
  - Secondary endpoints: changes in symptom scores using health-related QoL measures, additional efficacy outcomes, PK parameters, and clinical safety assessments
  - Exploratory biomarker analyses will evaluate the effects of JAK inhibition on circulating inflammatory cells (ie, T-cell subsets, B cells, natural killer cells, cytokines) and peripheral blood biomarkers of GVHD after transplant

Table 1. GRAVITAS-309 Study Endpoints

Part 1	Part 2
Primary	
• DLTs through Day 28 • Clinical safety and laboratory assessments	• ORR at Month 6
Secondary	
• C_{max}, C_{min}, T_{max}, $AUC_{0-\tau}$, and CI/F • ORR at Months 3, 6, and 12 • Time to response • DOR • OS • NRM • Proportion of patients with ≥50% reduction in daily CS use at Day 180 • Proportion of patients successfully tapered off all CS at Day 180 • Relapse rate • Time to primary hematologic disease relapse	• Changes in symptom scores using the LSS, QoL-SF-36 v2, EQ-5D-3L, PGIC, and PGIS • ORR at Months 3 and 12 • DOR • OS • NRM • Proportion of patients with ≥50% reduction in daily CS use at Day 180 • Proportion of patients successfully tapered off all CS at Day 180 • Relapse rate • Time to primary hematologic disease relapse • C_{min} in all patients • C_{max}, T_{max}, $AUC_{0-\tau}$, and CI/F (data permitting) • Data from clinical safety assessments (eg, AEs, infections)
Exploratory	
• Changes from baseline in lymphocyte subsets and inflammatory mediators in peripheral blood	• Changes from baseline in lymphocyte subsets and inflammatory mediators in peripheral blood
Endpoint	**Definition**
ORR	• Proportion of patients with a CR or PR
Time to response	• Interval between randomization and first response
DOR	• Interval between first response and cGVHD progression, death, or initiation of new systemic cGVHD therapy
OS	• Interval between date of randomization and date of death due to any cause
NRM	• Proportion of patients who died from causes other than relapse of their primary hematologic disease

AE, adverse event; $AUC_{0-\tau}$, area under the curve from time 0 to the last measured time point; cGVHD, chronic graft-versus-host disease; CI/F, apparent oral clearance; C_{max}, maximum observed concentration; C_{min}, minimum observed concentration; CR, complete response; CS, corticosteroid; DLT, dose-limiting toxicity; DOR, duration of response; EQ-5D-3L, EuroQol 5-Dimension Questionnaire 3 level; LSS, Lee cGVHD Symptom Scale; NRM, nonrelapse mortality; ORR, overall response rate; OS, overall survival; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PR, partial response; QoL-SF-36, Quality-of-Life Questionnaire 36-Item Short Form Survey version 2; T_{max}, time to C_{max}.

Statistical Analyses

- For Part 1, a sample size of 20 patients was chosen to allow for concurrent enrollment at 2 dose levels that have been previously characterized in other disease settings (ie, aGVHD)
  - Summary statistics will be provided for the safety and efficacy assessments by cohort
- For Part 2, a sample size of 236 patients (118 randomly assigned to each treatment group) will provide 90% power to detect a treatment difference of 0.20 in 6-month ORR between 2 treatment groups
  - A total sample size of 246 patients (123 per treatment group) compensates for an anticipated 4% early withdrawal rate
- Efficacy analyses will be performed on the intent-to-treat population
- Safety analyses will be conducted on all randomized patients who receive ≥1 dose of study drug
- The PK-evaluable population will include all patients who receive ≥1 dose of study drug and provide ≥1 postdose plasma PK sample

Conclusions

- **The GRAVITAS-309 trial is expected to provide comprehensive efficacy and safety data for itacitinib as initial therapy in combination with CS in patients with cGVHD**
- **Findings from GRAVITAS-309 are expected to yield insights into the role of JAK1 in the pathogenesis of cGVHD and may inform future treatment strategies**

Disclosures

AI has nothing to disclose. RM-Z, MB, and YY are employees of Incyte Corporation. SZP has nothing to disclose.

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