GRAVITAS-301: A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Itacitinib or Placebo in Combination With Corticosteroids for the Treatment of First-Line Acute Graft Versus Host Disease

Published: 02-08-2017
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Primary objective: Compare the efficacy of itacitinib in combination with corticosteroids versus placebo in combination with corticosteroids in terms of overall response rate (ORR) at Day 28 in subjects with aGVHD.Secondary objectives:- Compare the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON46651

Source
ToetsingOnline

Brief title
INCB 39110-301/GRAVITAS-301

Condition

- Haematological disorders NEC
- Autoimmune disorders

Synonym
Acute Graft-versus-Host Disease

Research involving
Human

Sponsors and support

Primary sponsor: Incyte Corporation
Source(s) of monetary or material Support: Incyte Corporation

Intervention

Keyword: Acute Graft-versus-Host Disease, Itacitinib, JAK1 inhibitor

Outcome measures

Primary outcome

ORR at Day 28, defined as the proportion of subjects demonstrating a complete response (CR), very good partial response (VGPR), or partial response (PR).

Secondary outcome

- Nonrelapse mortality (NRM) at Month 6, defined as the proportion of subjects who died due to causes other than malignancy relapse at Month 6.

- ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR at Days 14, 56, and 100.

- NRM at Months 9, 12, and 24.

-DOR (duration of response) for responders will be calculated. The DoR is defined from the time of the onset of response to loss of response. Subjects who died or discontinued will be censored at the death date or the previous assessment.

- Time to response, defined as the interval from treatment initiation to first response.

- Relapse rate of malignant and non malignant hematologic diseases, defined as the proportion of subjects whose underlying hematologic

disease relapses.

- Malignancy relapse-related mortality rate, defined as the proportion of subjects whose malignancy relapses and has a fatal outcome.

- Failure-free survival, defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for aGVHD, and have not demonstrated signs or symptoms of chronic graft-versus-host disease (cGVHD), at Month 6.

- Overall survival (OS), defined as the interval from study enrollment to death due to any cause.

- Clinical safety data (eg, AEs, infections) will be tabulated and listed.

- Cmax, Cmin, tmax, AUC, and CL/F.

- Incidence rate of secondary graft failure, defined as > 95% recipient cells any time after engraftment with no signs of relapse, OR retransplantation because of secondary neutropenia (< 0.5 × 109/L) and/or thrombocytopenia (< 20 × 109/L) within 2 months of transplant.

- Average and cumulative corticosteroid dose at Days 28, 56, 100, and 180; proportion of subjects who discontinue corticosteroids at Days 56 and 100.

- Proportion of subjects who discontinue immunosuppressive medications at Days 56 and 100.

- Incidence rate of aGVHD flares through Day 100.

- Incidence rate of cGVHD at Days 180 and 365.

Study description

Background summary

New treatments for the therapy of acute graft-versus-host disease (aGVHD) after allogeneic hematopoietic stem cell transplantation are urgently needed.

Hypothesis: Itacitinib will reduce aGVHD by suppressing inflammatory cytokine production
Itacitinib inhibits the JAK/STAT signaling pathway, which interrupts interferon signaling. This leads to a decreased expression of CXCR3 (chemokine receptor) in T-cells, which impairs T cell differentiation, activation and trafficking to GVHD target organs.

Study objective

Primary objective: Compare the efficacy of itacitinib in combination with corticosteroids versus placebo in combination with corticosteroids in terms of overall response rate (ORR) at Day 28 in subjects with aGVHD.

Secondary objectives:
- Compare the efficacy between treatment cohorts at a subsequent key clinical landmark.
- Compare additional response and longer-term efficacy outcomes between treatment cohorts.
- Assess the incidence and severity of adverse events (AEs) and serious adverse events.
- Evaluate the pharmacokinetics of itacitinib when administered in combination with corticosteroids.
- Evaluate the incidence of secondary graft failure.
- Evaluate the use and discontinuation of corticosteroids.
- Evaluate the use and discontinuation of immunosuppressive medications.
- Evaluate the incidence of aGVHD flares.
- Evaluate the incidence of cGVHD.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study

Intervention

Subjects will be randomized 1:1 to itacitinib 200 mg once daily (QD) plus corticosteroids or matching placebo plus corticosteroids.

Study burden and risks

There are about 27 visits. Until day 56 weekly visits, after that 1 visit per

28 days.
The following study procedures will be conducted:
Physical examination
Vital signs measurement
ECGs
GHVD assessment
pregnancy tests if applicable
blood draws
The patient needs to complete questionnaires

Risks: possible side effects of the study drug and study procedures.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Male or female, 18 years of age or older; outside the European Union, an older limit could apply depending on local regulation (eg, 20 years and older for Taiwan and Japan).
• Has undergone 1 allo-HSCT from any donor (related or unrelated with any degree of HLA matching) and any donor source (bone marrow, peripheral blood stem cells, or cord blood) for a hematologic malignancy or disorder. Recipients of myeloablative and reduced-intensity conditioning regimens are eligible.
• Clinically suspected Grade II to IV aGVHD as per MAGIC criteria, occurring after allo-HSCT and any GVHD prophylaxis regimen. Biopsies should be obtained to pathologically confirm aGVHD; in cases where a biopsy is negative, is unable to be obtained, or is clinically contraindicated, clinical suspicion of aGVHD by the treating physician is sufficient, provided that alternative diagnoses of drug effects or infection are adequately ruled out.
• Evidence of myeloid engraftment (eg, absolute neutrophil count >= 0.5 × 109/L for 3 consecutive assessments if ablative therapy was previously used). Use of growth factor supplementation is allowed.
• Be willing to avoid pregnancy or fathering children based on 1 of the following criteria:
- Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR >= 12 months of amenorrhea).
- Woman of childbearing potential who has a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
- Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
• Able to give written informed consent and comply with all study visits and procedures.
• Able to swallow and retain oral medication.

Exclusion criteria

• Has received more than 1 allo-HSCT.
• Has received more than 2 days of systemic corticosteroids for acute-GVHD.
• Presence of GVHD overlap syndrome.
• Presence of an active uncontrolled infection. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs, or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection.
• Known human immunodeficiency virus infection.
• Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment or at risk for HBV reactivation. HBV DNA and HCV RNA must be undetectable upon testing. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or

anti-hepatitis B core antibody positive. Prior test results obtained as part of standard of care that confirm a subject is immune and not at risk for reactivation (ie, hepatitis B surface antigen negative, surface antibody positive) may be used for purposes of eligibility and tests do not need to be repeated. Subjects with prior positive serology results must have negative polymerase chain reaction results. Subjects whose immune status is unknown or uncertain must have results confirming immune status before enrollment.
• Subjects with evidence of relapsed primary disease, or subjects who have been treated for relapse after the allo-HSCT was performed.
• Any corticosteroid therapy for indications other than GVHD at doses > 1 mg/kg per day methylprednisolone (or prednisone equivalent) within 7 days of randomization.
• Severe organ dysfunction unrelated to underlying GVHD, including:
- Cholestatic disorders or unresolved veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction).
- Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months of enrollment, New York Heart Association Class III or IV congestive heart failure, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that requires therapy.
- Clinically significant respiratory disease that requires mechanical ventilation support or 50% oxygen.
• Serum creatinine > 2.0 mg/dL or creatinine clearance < 40 mL/min measured or calculated by Cockroft Gault equation.
• Currently breast feeding.
• Receipt of live (including attenuated) vaccines or anticipation of need for such a vaccine during the study and within 6 months before randomization.
• Received Janus kinase (JAK) inhibitor therapy after allo-HSCT for any indication. Treatment with a JAK inhibitor before allo-HSCT is permitted.
• Treatment with any other investigational agent, device, or procedure, within 21 days (or 5 half-lives, whichever is greater) of enrollment. Subjects participating in a GVHD prophylaxis study or conditioning regimen should be discussed with the sponsor's medical monitor before enrollment.
• Any medical complications or conditions that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
• Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	itacitinib
Generic name:	itacitinib

Ethics review

Approved WMO Date:	02-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-000538-78-NL
ClinicalTrials.gov	NCT03139604
CCMO	NL62255.078.17

Study results

Results posted: 22-12-2020

Summary results
Trial never started

First publication
28-07-2020