A Phase III Randomized Open-label Multi-center Study of Ruxolitinib Versus Best Available Therapy in Patients With Corticosteroid-refractory Acute Graft vs. Host Disease After Allogeneic Stem Cell Transplantation (REACH 2) (CINC424C2301)

Published: 13-11-2017
Last updated: 12-04-2024

Primary: To compare the efficacy of ruxolitinib versus Investigator*s choice Best Available Therapy (BAT) in patients with grade II-IV steroid refractory- acute graft vs host disease assessed by Overall Response Rate (ORR) at the Day 28.Secondary:...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48922

Source
ToetsingOnline

Brief title
CINC424C2301 (REACH 2). Phase III trial with ruxolitiniob vs BAT for aGVHD

Condition

- Other condition

Synonym
graft vs host disease

Health condition

graft versus host disease naar stamcel transplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: Acute, Best Available Therapy, Graft versus host disease, Ruxolitinib

Outcome measures

Primary outcome

overall response rate

Secondary outcome

The primary and key secondary endpoints of the trial will be based on:

* Improvement or resolution of aGvHD manifestations (measures of body surface

area aGvHD skin rash, stool volumes or frequency per 24h time period, and serum

bilirubin levels)

* Reduction or cessation of required systemic corticosteroids

* Occurrence of graft failure

* Any progression or recurrence of the underlying hematologic disease for which

the alloSCT has been performed including malignancy

progression or relapse

* Incidence of chronic GvHD

Study description

Background summary

An allogenic stem cell transplantation bears the risk of the development of a graft-versus-host disease (GvHD). In a GvHD the donor cells are acting against the body of the patient. Immune cells of the donor attack the patient*s cells as they are considered foreign. A acute graft-versus-host disease (cGvHD) develops starting after the transplantation till 3 months. The disease may appear in all body parts. In most cases the disease is present in the skin, liver and GI tract. The disease damages tissues and organs and weakens the immune system of the body. This is why aGvHD patients are more susceptible for infections.
The purpose of the study is to assess the efficacy of ruxolitinib when added to immunosuppression therapy in patients with grade II-IV corticosteroid refractory aGvHD. The rationale of the study is based on current knowledge of aGvHD pathophysiology and published studies that ruxolitinib impairs human dendritic cell activation, modulates cytokine levels in dendritic cells, and deceases Tcell proliferation in murine models. Further, published data has shown that ruxolitinib has evidence of activity when added to immunosuppressive therapy in patients with steroid refractory acute graft versus host disease.

Study objective

Primary:
To compare the efficacy of ruxolitinib versus Investigator*s choice Best Available Therapy (BAT) in patients with grade II-IV steroid refractory- acute graft vs host disease assessed by Overall Response Rate (ORR) at the Day 28.

Secondary:
To compare the rate of durable ORR at Day 56 between ruxolitinib and best available therapy. ORR at Day 56 is defined as the proportion of all patients in each arm who achieve a complete
response (CR) or partial response (PR) at Day 28 and maintain a CR or PR at Day 56.

Study design

This trial is a randomized (1:1) phase III open label study of ruxolitinib compared to Investigator choice Best Available Therapy (BAT) in allogeneic stem cell transplant recipients with Grade II-IV steroid refractory acute graft vs. host disease. Patients randomized to the BAT arm are allowed to crossover to the ruxolitinib arm if they do not demonstrate complete or partial response after day 28 of randomization or if they lose their response thereafter and meet criteria for progression, mixed response, or no response, necessitating

new additional systemic immunosuppressive treatment for aGvHD.

Intervention

treatment with ruxolitinib of best available therapie

Study burden and risks

Risk: adverse effects of ruxolitinib or best available therapy

Burden:
Treatment phase (24 weeks)
weekly visits during week 1 till 8
4-weekly visits during week 12 till 24
followed by end of treatment visit and saftey FU
visit duration mostly 2-3 hours in teh treatment phase
Follow up phase (18 months):
visits on day 1 at Month 6 (after randomisation), month 9, month 12, month 18 and month 24.
In total 19 visits.

Physical examintation: every visit during treatment phase
Blood test (25mL per occassion): every visit during treatment phase.
Blood for biomarkers: 70 ml in total, PK 36 ml in total (extensive PK sampling at first 25 patients and all adolescents 60 ml in totaal).
pulmonary function test: if indicated
Questionnaires: FACT BMT and EQ-5D: every visit in treatment phase.
Optional biopsies: during treatment phase from affected tissue
Total study duration is 2 years.

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Male or female patients aged 12 or older
* Have undergone alloSCT from any donor source (matched unrelated donor, sibling, haplo-identical) using bone marrow, peripheral blood stem cells, or cord blood. Recipients of non-myeloablative, myeloablative, and reduced intensity conditioning are eligible
* Clinically diagnosed Grades II to IV acute GvHD as per standard criteria (Appendix 1) occurring after alloSCT requiring systemic immune suppressive therapy. Biopsy of involved organs with aGvHD is encouraged but not required for study screening.
* Evident myeloid and platelet engraftment (confirmed within 48h prior to study treatment start):
o absolute neutrophil count (ANC) > 1000/mm3 AND
o platelets * 20,000/ mm3
o Note: Use of growth factor supplementation and transfusion support is allowed.
* Confirmed diagnosis of steroid refractory aGvHD defined as patients administered high-dose systemic corticosteroids (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]), given alone or combined with calcineurin inhibitors (CNI) and either:
o A] Progressing based on organ assessment after at least 3 days compared to organ stage at the time of initiation of high-dose systemic steroid +/- CNI for the treatment of Grade II-IV aGvHD,
o OR B] Failure to achieve at a minimum partial response based on organ assessment after 7 days compared to organ stage at the time of initiation of high-dose systemic steroid +/- CNI for the treatment of Grade II-IV aGvHD,
o OR C] Patients who fail corticosteroid taper defined as fulfilling either one of the following criteria: 1. Requirement for an increase in the corticosteroid dose to methylprednisolone *2 mg/kg/day (or equivalent prednisone dose *2.5 mg/kg/day), OR 2. Failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days;see also section 5.2 in protocol

Exclusion criteria

1. Has received more than one systemic treatment for steroid refractory aGvHD.
2. Clinical presentation resembling de novo chronic GvHD or GvHD overlap syndrome with both acute and chronic GvHD features (as defined by Jagasia, et al. 2015).
3. Failed prior alloHSCT within the past 6 months.
4. Presence of an active uncontrolled infection including significant bacterial, fungal, viral or parasitic infection requiring treatment. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of progression are present. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.
5. Evidence of uncontrolled viral infection including CMV, EBV, HHV-6, HBV, or HCV based on assessment by the treating physician.
6. Presence of relapsed primary malignancy, or who have been treated for relapse after the alloHSCT was performed, or who may require rapid immune suppression withdrawal as pre-emergent treatment of
early malignancy relapse.
7. Previous participation in a study of any investigational treatment agent within 30 days of Screening or within 5 half-lives of the study treatment, whichever is greater.;see also protocol section 5.3

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-05-2018

Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Jakavi
Generic name:	ruxolitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-11-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	11-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR201600258433-NL
ClinicalTrials.gov	NCT02913261
CCMO	NL63562.056.17