A phase III randomized open-label multi-center study of ruxolitinib vs. best available therapy in patients with corticosteroid-refractory chronic graft vs host disease after allogeneic stem cell transplantation (REACH 3) (CINC424D2301)

Published: 21-06-2017
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Primary: To compare the efficacy of ruxolitinib versus Investigator*s choice Best Available Therapy (BAT) in patients with moderate or severe SR-cGvHD assessed by Overall Response Rate (ORR) at the Cycle 7 Day 1 visit.Secondary: To compare the rate...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50350

Source
ToetsingOnline

Brief title
CINC424D2301 (REACH3). Phase III trial with ruxoloitinib vs BAT for cGVHD

Condition

- Other condition

Synonym
Graft vs host disease

Health condition

Graft versus host disease na stamcel transplantatie

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Best available therapy, Chronic, Graft versus host disease, Ruxolitinib

Outcome measures

Primary outcome

Overall response rate

Secondary outcome

Failure free survival, change in modified Lee cGvHD Symptom Scale score. Best overall response, duration of response, overall survival, non-relapse mortality, proportion of patients with >=50% reduction in the daily steroid dose at Cycle 7 Day 1, proportion of patients who successfully tapered off all steroids at Cycle 7 Day 1. Cumulative incidence of Malignancy Relapse/Recurrence. Change in FACT-BMT and EQ-5D. PK of ruxolitinib. Safety and tolerability of ruxolitinib and BAT. Medical resource utilization.

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 chronic graft-versus-host disease (cGvHD) develops starting from 2-3 months after the transplantation. It may last for years. The disease may appear in all body parts. In most cases the disease is present in the skin, liver, mouth and eyes. The disease damages tissues and organs and weakens the immune system of the body. This is why cGvHD 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 moderate to severe corticosteroid refractory cGvHD. The rationale of the study is based on current knowledge of cGvHD 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 chronic graft versus host disease.

Study objective

Primary:
To compare the efficacy of ruxolitinib versus Investigator*s choice Best Available Therapy (BAT) in patients with moderate or severe SR-cGvHD assessed by Overall Response Rate (ORR) at the Cycle 7 Day 1 visit.
Secondary:
To compare the rate of failure free survival (FFS) and the change in the modified Lee cGvHD Symptom Scale score between treatment groups. Other indicators of efficacy. Cumulative incidence of Malignancy Relapse/Recurrence. Change in FACT-BMT and EQ-5D. PK of ruxolitinib. Safety and tolerability of ruxolitinib and BAT. Medical resource utilization.

Study design

This is a randomized open-label multi-center study of ruxolitinib versus best available therapy (BAT). Treatment cycles of 4 weeks. Patients randomized to the BAT arm are allowed to cross over to the ruxolitinib arm after the Cycle 7 Day 1 visit.
Maximum duration of treatment 3 years.
Follow-up for survival up to 3 years on study in subjects discontinuing study treatment within 3 years for other reasons than complete or partial response.
Approx. 324 subjects.

Intervention

Treatment with ruxolitinib or best available therapy.

Study burden and risks

Risk: Adverse effects of ruxolitinib or best available therapy.
Burden: Cycles of 4 weeks. 4 visits during cycle 1. Visits on day 1 of every cycle (cycle 2-7). Visits on day 1 of every 3rd cycle (cycle 9 and above).
Visit duration mostly 2-3 hours.
Physical examination: every cycle.
Blood tests (25 ml/occasion): every cycle.
Blood for biomarkers: 170 ml in total, PK 24 ml in total (extensive PK sampling in 8 adult and 4 adolescnet subjects 64-88 ml in total).
Pulmonary function test: nearly all visits.
Dexascan (<18 yearsold): 5-6 times
Questionnaires Modified Lee Symptom Scale, FACT BMT, EQ-5D, PGIS, PGIC: nearly every visit.
Optional biopsies during treatment from affected tissue.

Contacts

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Scientific
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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

•Female and male patients >= 12 years old.
•Having undergone allogenic stem cell transplantation, see protocol section 5 for details.
•Absolute neutrophil count > 1000/mm3 and platelet count > 25,000/ mm3.
•Patients with clinically diagnosed cGvHD staging of moderate to severe according to NIH Consensus Criteria, see protocolsection 5 for details.
•Currently receiving systemic or topical corticosteroids for the treatment of cGvHD for a duration of < 12 months prior to Cycle 1 Day 1, and have a confirmed diagnosis of corticosteroid refractory cGvHD defined per 2014 NIH consensus criteria irrespective of the concomitant use of a calcineurin inhibitor (CNI), see protocol section 5 for details.
•ECOG performance status 0-1-2 or Lansky performance score 60-100%.
•Patient must accept to be treated with only one of the following BAT (best available therapy) options. Additions and changes are allowed during the course of the study, but only with BAT from the following options: extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, everolimus or sirolimus, infliximab, rituximab, pentostatin, imatinib or ibrtinib. Concomitant use of CNI and steroids is allowed.

Exclusion criteria

•Having received 2 or more systemic treatment for cGvHD in addition to corticosteroids ± CNI for cGvHD.
•Overlap syndrome, see protocol section 5 for details.
•Treated with prior JAK inhibitors for acute GvHD, see protocol section 5 for exceptions.
•Failed prior allogenic stem cell transplantation within the past 6 months.
•Relapsed primary malignancy, or who having been treated for relapse after the allogenic stem cell transplantation was performed.
•History of progressive multifocal leuko-encephalopathy.
•Active uncontrolled bacterial, fungal, parasitic, or viral infection, see protocol section 5 for details.
•Mechanical ventilation or resting O2 saturation <90%.
•Any corticosteroid therapy for indications other than cGvHD at doses >1 mg/kg/day methylprednisolone or equivalent within 7 days of Cycle 1 Day 1.
•Treatment with medications that interfere with coagulation or platelet function, see protocol section 5 for details.
•Pregnancy, lactation, insufficient contraception for females of childbearing potential, see protocol section 5 for details.
•For male patients randomized to BAT: Sexually active males, unless they use a

condom during intercourse, see protocol section 5 for details.

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:	Recruiting
Start date (anticipated):	27-02-2018
Enrollment:	12
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:	21-06-2017
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	25-10-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	15-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	08-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2016-004432-38-NL
ClinicalTrials.gov	NCT03112603
CCMO	NL61887.041.17