A Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric patients with grade II-IV acute graft vs. host disease after allogeneic hematopoietic stem cell transplantation

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Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48950

Source
ToetsingOnline

Brief title
CINC424F12201 (REACH 4).

Condition

- Other condition

Synonym
graft versus 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: Acute, Graft versus Host Disease, Pediatric, Ruxolitinib

Outcome measures

Primary outcome

Phase I

To assess pharmacokinetic (PK) parameters of ruxolitinib for patients with

aGvHD and SR-aGvHD and define an age

appropriate RP2D for each of the groups 2-4

* Group 2: age *6y to <12y

* Group 3: age *2y to <6y

* Group 4: age *28days to < 2y

Phase II

To measure the activity of ruxolitinib in patients with aGvHD or SR-aGvHD

assessed by Overall Response Rate (ORR) at Day 28.

Secondary outcome

The key secondary endpoint is to assess the rate of durable ORR at Day 56 by

measuring

the proportion of all patients who achieve a CR or PR at Day 28 and maintain a

CR or PR

at Day 56.

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.
Systemic steroids alone or in combination with calcineurin inhibitor have remained SOC as initial systemic treatment of aGvHD grades II-IV over 3 decades (Ruutu 2014). Unfortunately, only 30*50% of children respond to corticosteroids as initial therapy, and optimal initial or second-line therapies have not yet been determined (Carpenter and Macmillan 2010).
Treatments that are currently used for Grade II-IV steroid refractory aGvHD (SR-aGvHD) are mostly off-label and although they demonstrate initial responses in approximately 50% of patients, they are associated with aGvHD flare during attempted steroid taper. These second line treatments include the following: ATG, extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab. Management of aGvHD flare necessitates administration of further high dose systemic corticosteroids over

a more prolonged
time period and/or additional new systemic immunosuppressive therapy leading to lifethreatening
infections, and/or malignancy recurrence, with resultant two year survival rates ranging only approximately 20-30% (Martin et al 2012). As such, more effective treatment for
aGvHD and SR-aGvHD grades II-IV in pediatric patients represents a very high unmet medical
need.

Study objective

The purpose of the study intends to assess safety, activity and pharmacokinetics of ruxolitinib treatment with corticosteroids in treatment-naïve and steroid refractory (SR)- acute Graft versus Host Disease (aGvHD) patients aged *28 days to <18 years of age.
The rationale of the study is based on current knowledge of acute graft vs. host disease pathophysiology and published studies showing that ruxolitinib impairs antigen presenting cell function, inhibits donor T cell proliferation, suppresses adverse cytokine production,
and improves survival and disease manifestations in GvHD mouse models. Further, published data has shown that ruxolitinib has evidence of clinical efficacy when added to immunosuppressive therapy in patients with steroid refractory acute graft vs. host disease.
Clinical studies using ruxolitinib (10mg BID) alone or in comparison to best available therapy are currently underway in the SR-aGvHD setting for adult patients and adolescents * 12 years of age. Recent data with ruxolitinib in SR-aGvHD pediatric patients (ages 1.6 y/o-16.4 y/o) have shown encouraging overall response rates compared to corticosteroids +/- CNI alone (Khandelwal 2017).

Study design

This trial is a Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric allogeneic stem cell transplant (alloSCT) recipients with grade II-IV acute graft vs. host disease. Patients will be enrolled into 4 groups based on age (Group 1 (Age *12 years to < 18 years), Group 2 (Age *6 years to < 12 years), Group 3 (Age *2 years to < 6 years) and Group 4 (Age *28 days to <2 years) to allow appropriate dosing based on available data. Group 1, being treated with the same dose as the ongoing registration trial (CINC424C2301 using 10mg BID), will be enrolled directly into the Phase II. The remaining groups will be enrolled in Phase I: Group 2 will have a starting dose of 5mg BID, Group 3 will have a starting dose of 4mg/m2 BID, and the starting dose of Group 4 will be determined based on the PK data collected from Groups 1-3.During the Phase I, the PK, safety and activity data for Groups 2-4 will be reviewed by the data monitoring committee

(DMC). Should all of these parameters be considered appropriate by the DMC, the starting dose for each group will be confirmed as the RP2D for each age group, and
then used as the starting dose for all future patients of that age group enrolled into the Phase II.All patients enrolled in the study will be treated for 24 weeks(approximately 6 months) or until early discontinuation. All patients will also be followed for additional 18 months (total duration of study = up to 2 years from enrollment). Should the occurrence of aGvHD flare require treatment re-initiation or should ruxolitinib not be discontinued by the end of 24 weeks due to extended tapering, patients may continue to taper ruxolitinib beyond 24 weeks up to a maximum of 48 weeks (approximately 12 months).

Intervention

treatment with ruxolitinib

Study burden and risks

Risk: side effects of ruxolitinib
Burden:
Treatment phase: screening followed by 4-week cycles. Weekly visits during cycle 1 and 2. Visits on day 1 of each cycle (cycle 3-6). Total duration of treatment phase is 24 weeks after randomization.
The follow-up phase will follow after end of treatment and safety follow-up. Follow-up phase visit on day 1 of month 12 (after randomization), month 18 and month 24.
Total 16 visits. Duration per visit is usually 2-3 hours in treatment phase.
Physical examination: every visit in treatment phase.
Blood tests (11-25 ml / times): each visit in treatment phase.
Blood for biomarkers: quantity depending on age cohort
Dexa scan: 4 visits
Questionnaire (1): 3 visits (only if patient is given medication in oral solution form)

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

For a full list of inclusion criteria, refer to Section 5.1. Key inclusion criteria include:
* Male or female patients age *28 days and <18 years at the time of informed consent.
* Patients who 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 myeloablative or reduced intensity conditioning are eligible.
* Patients with a confirmed diagnosis of grades II-IV aGvHD within 48 hours prior to study treatment start. Biopsy confirmation of aGvHD is recommended but is not required. Enrollment should not be delayed awaiting biopsy or pathology results. Should the biopsy results not confirm aGvHD, however, the patient must discontinue from the study if study treatment has already been started. Patients may have either: Treatment-naïve aGvHD as per Table 8-2 (Harris et al. 2016) OR Steroid refractory aGvHD as per institutional criteria, and the patient is currently receiving systemic corticosteroids.
* Evident myeloid engraftment with ANC > 1,000/*l and platelet count >20,000/*l. (Use of growth factor supplementation and transfusion support is allowed.)

Exclusion criteria

For a full list of exclusion criteria, refer to Section 5.2. Key exclusion criteria include:
* Has received the following systemic therapy for aGvHD: a) Treatment-naïve aGvHD patients have received any prior systemic treatment of aGvHD except for a maximum 72h of prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of acute GvHD. Patients are allowed to have received prior GvHD prophylaxis which is not counted as systemic treatment (as long as the prophylaxis was started prior to the diagnsosis of aGvHD);
OR
b) SR-aGvHD patients have received two or more prior systemic treatments for aGvHD in addition to corticosteroids
* 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).
* Failed prior alloSCT within the past 6 months.
* Presence of relapsed primary malignancy, or who have been treated for relapse after the alloSCT was performed, or who may require rapid immune suppression withdrawal of immune suppression as pre-emergent treatment of early malignancy relapse.
* Acute GvHD occurring after non-scheduled donor leukocyte infusion (DLI) administered for pre-emptive treatment of malignancy recurrence. Note: Patients who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse are eligible.
* Any corticosteroid therapy for indications other than aGvHD at doses > 1 mg/kg/day methylprednisolone (or equivalent prednisone dose 1.25 mg/kg/day) within 7 days of Screening. Routine corticosteroids administered during conditioning or cell infusion is allowed.
* Patients who received JAK inhibitor therapy for any indication after initiation of current alloSCT conditioning.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	18-12-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	16-04-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR201800042255-NL
ClinicalTrials.gov	NCT03491215
CCMO	NL65847.000.18