A phase II, open-label, non-controlled, intra-patient dose-escalation study to characterize the pharmacokinetics after oral administration of eltrombopag in pediatric patients with refractory, relapsed or treatment naïve severe aplastic anemia or recurrent aplastic anemia (CETB115E2201)

Published: 08-08-2017
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To characterize the PK of eltrombopag at steady state after oral administration in pediatric patients with SAA.Secondary (key only, see protocol page 40-41 for all objectives): Safety and tolerability. Efficacy (overall response rate ORR).

Ethical review	Approved WMO
Status	Will not start
Health condition type	Anaemias nonhaemolytic and marrow depression
Study type	Interventional

Summary

ID

NL-OMON50357

Source
ToetsingOnline

Brief title
ETB115E2201

Condition

- Anaemias nonhaemolytic and marrow depression

Synonym
severe aplastic anemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: aplastic anemia, children, cyclosporine, eltrombopag, hATG

Outcome measures

Primary outcome

Eltrombopag PK parameters at week 2 and 12 (incl. highest dose level at

steady-state).

Secondary outcome

(key only, see protocol page 40-41 for all objectives) Adverse events.

Proportion of patients with an overall response at week 12, 26, 52, 78 and

proportion of patients with a platelet response.

Study description

Background summary

Immunosuppressive treatment (IST) is the standard of care for the treatment of aplastic anemia patients who are not candidate for HSCT with an HLA identical donor. Related to SKION children are treated with a combination of cyclosporine A and hATG (horse ATG). This treatment was chosen because of results of the NCI (Scheinberg et.al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia, NEJM, 365:430*438) showing that horse ATG has better remision percentages compared to rabbit ATG.
There are several limitations of IST in severe aplastic anemia (SAA), e.g. the majority of the responses observed following initial IST are partial with only

a few patients achieving normal blood counts, 1/3 of patients are refractory to initial IST, hematologic relapses occur in 35% of responders following initial response to IST, among relapsed patients chronic use of cyclosporine A is not infrequent which often leads to toxicities and clonal evolution is still observed in 10-15% of patients.
In order to address these limitations, efforts to improve initial IST in treatment-naïve patients with the addition of mycophenolate mofetil and sirolimus to standard horse anti-thymocyte globulin (hATG) /cyclosporine or use of lymphocytotoxic agents have not yielded the expected better outcomes when compared to standard (h-ATG/cyclosporine).
The most important advance in SAA in the recent years has been the seminal observation that a thrombopoietin receptor agonist, eltrombopag, has activity in SAA, as recenty published: Townsley et.al. Eltrombopag added to standard immunosuppression for aplastic anemia, NEJM, 376;16, april 20 2017. Eltrombopag is registered for adults with SAA. In this study the same will be done in children.
Previous research focusing on safety and dosing of eltrombopag was done in children with ITP. Eltrombopag is registered for this indication for children older than 1 year.
The lack of availability of anti-thymocyte globulin (hATG) in several countries has left a large proportion of patients with SAA with limited treatment options and poor outcome. In this context, the combination of cyclosporine and eltrombopag, 2 therapies with different modes of action, is an attractive therapeutic option to address this unmet medical need, with the possible addition of hATG. In the Netherlands hATG is available and part of the standard of care.
The main objective of this study is to assess the safety and efficacy of eltrombopag and cyclosporine and in the Netherlands with the addition of hATG for the treatment-naïve SAA patients and subject with relapsed or recurrent disease.

Study objective

To characterize the PK of eltrombopag at steady state after oral administration in pediatric patients with SAA.
Secondary (key only, see protocol page 40-41 for all objectives):
Safety and tolerability. Efficacy (overall response rate ORR).

Study design

Phase II, open-label, non-controlled, intra-patient dose-escalation study.
Eltrombopag plus cyclosporine plus or minus hATG. Escalation part (eltrombopag) 10 weeks, maintenance up to 6 months. Evaluation of efficacy at 6 months. Responders may remain on eltrombopag plus cyclosporine up to at least month 54.
3 cohorts (approx. 20 subjects each):
* A.

1. For subjects who have been pretreated for SAA. Eltrombopag plus cyclosporine plus ATG. ATG only during first 4 days. I.V., duration 4 to 8 hours, max. up to 24 hours. On day 1 of the treatment period treatment with eltrombopag and cyclosporine will be initiated as well. Eltrombopag as tablets or soluble powder. Cyclosporine in capsules or in a drinkable liquid.
2. For subjects who have been pretreated for SAA. Eltrombopag plus cyclosporine. For the rest cohort A1 will be treated in the same way as cohort A1. Investigator chooses allocation of the subject to Cohort A1 or A2.
* B. For treatment-naive subjects with SAA. Eltrombopag plus cyclosporine plus ATG. Cohort B will be treated in the same way as cohort A1.
Non-responders will stop study medication at week 26 and will enter the follow-up period, followed by the long-term follow-up period (4 years in total).
Approx. 60 subjects.

Intervention

Treatment with eltrombopag, cyclosporine and possibly hATG.

Study burden and risks

Risk: Adverse effects of eltrombopag in combination with cyclosporine ± hATG.
Burden: Screening 4 weeks, treatment with eltrombopag and cyclosporine (as long as subjects benefits from treatment) ± hATG (for first 4 days). Total study duration approx. 4,5 years.
35 visits in 4,5 years.Duration mostly 4 hours.
Physical examination: 34 times.
Blood tests: safety every visit (5-10 ml/occasion); biomarkers approx. 9 times (2,0 ml/occasion); PK approx. 30 ml in total); cyclosporine levels 14 times (5 ml/occasion).
Pregnancy test urine (if relevant): 29 times.
Bone marrow sample: 9 times.
ECG: cycle 4 times.
Questionnaire: 10 times.
Optional storage and use of the remaining blood and tissue for future research.

Contacts

Public
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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)
Children (2-11 years)

Inclusion criteria

* Cohort-specific criteria: see protocol page 46.
* Male and female 1 up to 18 years.
* Aplastic anemia.
* Hematopoietic stem cell transplantation not suitable or available as a treatment option or has been refused by the subject.
* Bone marrow aspirate and biopsy at any time during the 4 weeks prior to first dose of eltrombopag.
* Normal karyotype with FISH for chromosomes 7 and 8.
* Performance status score: Karnofsky *50 for patients 16 years of age and older or Lansky *50 for patients below 16 years of age.

Exclusion criteria

* Prior and/or active history of several diseases, see protocol page 47 for details.
* Active infection not responding to appropriate therapy.
* Prior eltrombopag or other thrombopoietin receptor (TPO-R) agonist treatment for at least 2 months and a lack of response.
* Impaired cardiac function. See protocol page 48 for details.

* Pregnant or nursing (lactating) women.
* Females of childbearing potential and males not using adequate contraception.
See protocol page 48 for more details.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ATGAM
Generic name:	Horse ATG
Product type:	Medicine
Brand name:	Cyclosporine A
Generic name:	Cyclosporine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Revolade
Generic name:	Eltrombopag
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-11-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	29-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	27-07-2020
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	EUCTR2015-003166-91-NL
ClinicalTrials.gov	NCT03025698
CCMO	NL61619.078.17