A Three-part Study of Eltrombopag in Thrombocytopenic Subjects with Myelodysplastic Syndromes or Acute Myeloid Leukemia (Part 1: open-label, Part 2: randomized, double-blind, Part 3: extension).;ASPIRE: A Study of EltromboPag In Myelodysplastic SyndRomes and AcutE Myeloid Leukemia

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Part 1 (open-label, 8 week): safety and tolerability of eltrombopag, optimal dose escalation scheme for use in Part 2, PK.Part 2: Primary: the reduction in the number of clinically relevant thrombocytopenic events (*Grade 3 hemorrhagic adverse...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON39136

Source
ToetsingOnline

Brief title
ASPIRE

Condition

- Haematological disorders NEC

Synonym
thrombocytopenia; decreased number of thrombocytes

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AML, eltrombopag, MDS, thrombocytopenia

Outcome measures

Primary outcome

The composite primary endpoint of the randomized part of the study consists of the following: the proportion of * Grade 3 hemorrhagic events, or platelet counts <10 Gi/L, or platelet transfusions.

Secondary outcome

Number of platelet transfusions, effects on hematologic improvement, platelet counts, bleeding symptoms, disease progression, overall survival. Safety and tolerability. Medical resource utilization. quality of life. Population PK.

Study description

Background summary

The standard therapy for thrombocytopenia in patients with malignancies is dependent upon the degree of thrombocytopenia, the cause and whether or not bleeding is present. Guidelines recommend platelet transfusions if platelet counts are <10Gi/L, or if an acute thrombocytopenic hemorrhage requires immediate elevation in platelet counts. Patients with less severe thrombocytopenia or without bleeding may be followed closely with a watch and wait approach. If thrombocytopenia is due to acute chemotherapy, the next cycle

of chemotherapy may either be dose reduced or delayed until megakaryopoiesis has recovered.
General limitations and risks associated with platelet transfusions include a short-lived therapeutic effect (1-5 days) and mild to severe transfusion reactions or the development of refractoriness to platelet transfusions. Therefore, platelet transfusions are not a viable option to maintain platelet counts sufficient to reduce hemorrhagic risk over time or to enable patients to receive chemotherapy.
Eltrombopag olamine is an orally bioavailable, small molecule thrombopoietin receptor agonist that is being studied in patients with medical disorders associated with thrombocytopenia. It has been approved for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) in adults (after splenectomy or if refractory for other treatments). In myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), megakaryopoiesis can be impaired in both a quantitative (lack of megakaryocytes), and qualitative way (increased apoptosis in megakaryocytes from patients with MDS). Interestingly, increased apoptosis of megakaryocytes has also been observed in ITP. Based on the pathophysiology of thrombocytopenia in MDS and AML and based on eltrombopag*s known mechanism of action, it is very likely that eltrombopag will be able to increase platelet counts and reduce thrombocytopenic sequelae (platelet transfusions and haemorrhages) in patients with MDS and AML.

Study objective

Part 1 (open-label, 8 week): safety and tolerability of eltrombopag, optimal dose escalation scheme for use in Part 2, PK.
Part 2:
Primary: the reduction in the number of clinically relevant thrombocytopenic events (*Grade 3 hemorrhagic adverse events, or platelet counts <10 Gi/L, or platelet transfusions).
Secondary: need for platelet transfusions, effects on hematologic improvement, platelet counts, bleeding symptoms, disease progression, overall survival.
Safety and tolerability. Medical resource utilization. quality of life.
Population PK.
Part 3: Long-term durability of clinical benefit, safety and tolerability.
Overall survival.

Study design

Phase II study in 3 sequential parts. Subjects who complete the treatment period for Part 1 or Part 2
may enter Part 3.

Part 1 (open-label): 6-10 patients, 8 weeks treatment with eltrombopag 100 mg/day. Dose escalation up to 300 mg/day allowed. Supportive care allowed, no disease modifying treatment or chemotherapy.

Part 2 (randomized, double-blind): 140 patients, 12 weeks supportive care randomisation (2:1) to eltrombopag or placebo. Start dose eltrombopag 100 mg/day. Dose escalation up to 300 mg/day allowed. No disease modifying treatment or chemotherapy.

Part 3 (open-label extension study): All subjects will receive eltrombopag. Supportive care allowed (incl. azacitidine, decitabine, lenalidomide and chemotherapy).

Maximal duration approx. 1 year in total.

Note: Subjects who do not enter Part 3 will undergo weekly follow-up assessments for 4 weeks following the last dose of study medication and monthly assessments for survival for 1 year.

Intervention

Treatment with eltrombopag (part 1 and 3) or eltrombopag or placebo (part 2).

Study burden and risks

Risk: Adverse effects of study medication. Supportive treatment accepted.
Burden: Part 1 and 2 weekly visits during 8 or 12 weeks resp.. Part 3: visits every 1-2 weeks during rest of the year.
Every visit: pulse, BP and blood tests (10-30 ml/visit).
Physical examination and ECG: 2x during part 1 or 2 and end of study.
Pregnancy test (if relevant): 2x.
Bone marrow sample: if needed at baseline (if no recent sample available) and every 3 months during part 3.
Questionnaires: quality of life: part 1 2x, part 2 every visit and during part 3 every 4 weeks.
Optional: pharmacogenetic research (1x 10 ml blood).

Contacts

Public
GlaxoSmithKline BV

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Age 18 years and above.
* MDS or AML (bone marrow blasts *50%) with thrombocytopenia due to bone marrow insufficiency from the disease or prior treatment. Subjects with transient thrombocytopenia due to active treatment with disease modifying agents or chemotherapy (except for hydroxyurea) are excluded.
* Grade 4 thrombocytopenia (platelet counts <25 Gi/L) due to bone marrow insufficiency (or platelet count *25 Gi/L due to platelet transfusion). In addition, subjects must have had at least one of the following during the 4 week screening period: platelet transfusion, or symptomatic bleeding or platelet count <10 Gi/L. Subjects whose thrombocytopenia below 10 Gi/L is due to causes other than bone marrow insufficiency are not eligible.
* Prior systemic treatment for malignancy, with the exception of hydroxyurea, must have been discontinued 4-8 weeks prior to entry into the study (see protocol for details).
* Subjects with a prior stem cell transplant (SCT) must have relapsed after the SCT.
* Female participants and female partners of male participants of child-bearing potential (after menarche): subject must not be sexually active or is practicing an acceptable method of contraception.

Exclusion criteria

* MDS and an IPSS of low or intermediate-1 risk.
* Acute promyelocytic or megakaryocytic leukemia or AML secondary to a myeloproliferative neoplasm.
* History of treatment with romiplostim or other TPO-R agonists.

* Leukocytosis *25,000/uL.
* Pregnancy and breast feeding. Inadequate contraception, if relevant.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-04-2013
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Revolade
Generic name:	eltrombopag
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	04-01-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
Other	clinicaltrials.gov; registratienummer n.n.b.
EudraCT	EUCTR2011-000114-19-NL
CCMO	NL39253.029.11