A Multicenter Phase 3 Randomized, Open-Label Study of Bosutinib versus Imatinib in Adult Patients with Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia

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Primary: To compare the proportion of patients demonstrating Major Molecular Response (MMR) at 12 months (48 weeks) in the bosutinib arm with that of the imatinib arm in newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase (CP)...

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

Summary

ID

NL-OMON44373

Source
ToetsingOnline

Brief title
Avillion_CML_AV001

Condition

- Other condition
- Leukaemias

Synonym
Chronic myelogenous leukemia, CML

Health condition

hematologic, Chronic myelogenous leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Avillion Development 1 Limited
Source(s) of monetary or material Support: Avillion Development 1 limited

Intervention

Keyword: Bosutinib, Chronic Myelogenous Leukemia, Imatinib, tyrosine kinase inhibitor

Outcome measures

Primary outcome

Efficacy: Efficacy will be determined by analysis of physical examination findings, peripheral blood and bone marrow; the primary efficacy analysis will be performed at the end of the Core Treatment Phase of the study. The Core Treatment Phase is the first 12 months (48 weeks) of the study on a per patient basis. Automated complete blood counts (CBCs), differential counts (with manual confirmation of abnormalities), bone marrow differentials, cytogenetics, and mortality will be used to determine the response to treatment. Cytogenetic, molecular, and hematologic response rates will be estimated for all randomized patients.

Primary Efficacy Endpoint:

* The primary efficacy endpoint is major molecular respons (MMR) at 12 months (48 weeks) in Ph+ CML patients with b2a2-and/or b3a2 transcripts. MMR is defined as *0.1% BCR-ABL1 on the international scale (IS) by real-time quantitative polymerase chain reaction (RQ-PCR).

Secondary outcome

Secondary Efficacy Endpoints:

* Major molecular respons (MMR) by 18 months.

* Duration of MMR.

* Complete cytogenetic response (CCyR) by 12 months.

* Duration of CCyR.

* Event free survival (EFS).

* Overall survival (OS).

Exploratory Efficacy Endpoints:

* MMR at 3, 6, 9 and 18 months.

* MMR at 12 months in the Philadelphia chromosome unrestricted (i.e., Ph+ and Ph-) patient population.

* MR1 and MR2 at 3 months and 6 months respectively.

* MR4 and MR4.5 at 3, 6, 9 and 12 months.

* Time to MMR.

* Cumulative CHR in both Ph+ and Philadelphia chromosome unrestricted (Ph+ and Ph-) patient population.

* Time to CCyR.

* Time to transformation to AP and blast phase BP on treatment.

* Type of mutations present at treatment completion/discontinuation or suboptimal response in each treatment group.

* Presence of newly observed BCR-ABL mutations in patients post-baseline and

correlation with response to treatment in imatinib and bosutinib treatment groups.

Pharmacokinetic Data

* Population PK of bosutinib.

* Correlations between trough concentrations of bosutinib and key efficacy and safety parameters.

Safety:

Safety will be assessed on an ongoing basis by physical examination including measurement of vital signs, laboratory assessments, standard safety evaluations (electrocardiograms) for monitoring of QTc interval changes and echocardiograms/MUGA scans for monitoring ventricular function) and recording of adverse events and serious adverse events. Adverse events will be graded according to the NCI CTC version 4. * Discontinuations due to AEs will be considered the main comparative safety endpoint for AEs.

Quality of Life:

* Patient reported health outcomes and QoL will be assessed using Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) and EuroQol-5D (EQ-5D) questionnaires.

Study description

Background summary

CML is the fourth most commonly occurring adult leukemia. CML is a clonal myeloid neoplasm in which the leukemic cells in over 95% patients have a reciprocal translocation between chromosomes 9 and 22 t(9;22)(q34;q11), the consequence of which is the generation of the Philadelphia (Ph) chromosome. The molecular product of the t(9;22) translocation is the BCR-ABL1 oncogene, which encodes the constitutively activated BCR-ABL1 kinase that activates several downstream signaling pathways that mediate myeloproliferation, resistance to apoptosis and genetic instability. The transition of patients with CML from CP to BP with an intermediate AP is becoming less standard with the chief determinants of survival being disease stage and TKI responsiveness.

Study objective

Primary: To compare the proportion of patients demonstrating Major Molecular Response (MMR) at 12 months (48 weeks) in the bosutinib arm with that of the imatinib arm in newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase (CP) chronic myelogenous leukemia (CML) patients harbouring b2a2 and/or b3a2 transcripts.

Secondary:
* To evaluate MMR by 18 months in the bosutinib treatment group compared with the imatinib treatment group.
* To evaluate the duration of MMR in the bosutinib treatment group compared with the imatinib treatment group.
* To estimate the proportion of patients demonstrating a cytogenic response (CCyR) by 12 months in both treatment groups.
* To evaluate the duration of CCyR in both treatment groups.
* To evaluate event free survival (EFS) in both treatment groups.
* To evaluate overall survival (OS) in both treatment groups.
* To assess the population pharmacokinetics (PK) of bosutinib administered once daily.
* To assess correlations between trough concentrations of bosutinib and key efficacy and safety parameters.
* To evaluate the safety profile of bosutinib and imatinib treatments.

Exploratory:
* To evaluate MMR at 3, 6 and 9 months and at 18 months in both treatment groups.
* To evaluate MMR at 12 months in both treatment groups in the Philadelphia chromosome unrestricted (i.e., Ph+ and Philadelphia chromosome negative [Ph-]) patient population.
* To evaluate MR1 and MR2 at 3 months and 6 months respectively in both treatment groups.
* To evaluate MR4 and MR4.5 at 3, 6, 9 and 12 months in both treatment groups.

* To evaluate time to MMR in the bosutinib treatment group compared with the imatinib treatment group.
* To evaluate the proportion of patients with cumulative complete hematologic response (CHR) in both treatment groups in both Ph+ and Philadelphia chromosome unrestricted (i.e., Ph+ and Ph-) patient population.
* To evaluate the time to CCyR in both treatment groups.
* To estimate the time to transformation to accelerated phase (AP) and blast phase (BP) on treatment in both treatment groups.
* To evaluate patient-reported outcomes, including quality of life (QoL), using Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) and EuroQol-5D (EQ-5D), in both treatment groups.
* To evaluate the type of BCR-ABL mutations present at treatment completion or discontinuation, or in case of suboptimal response in both treatment groups.
* To investigate the presence of newly observed BCR-ABL mutations in patients with sub-optimal response in both treatment groups.

Study design

Phase 3, 2-arm, randomized, open label trial. Patients will be randomized to receive bosutinib or imatinib for the duration of the study. Only laboratory and pathology staff will be blinded for treatment subjects have received.

Intervention

Patienten were randomised (1:1) on either 400 mg/day imatinib or 400 mg/day bosutinib, to be taken as tablets during a meal. Dosing may be optimised depending on efficacy and side effects. This means if insufficent efficacy, but few side effects the dose may be stepwise increased or if sufficient efficacy, but to extensive side effects the dose may stepwise be reduced.

Study burden and risks

This is a fase III study that includes some additional safety lab, bone morrow aspirates and additional visits as compared to standard of care treatment. Imatinib is a well-known drug that is commonly used as one of several tyrosine kinase inhibitors as treatment for CML. Unfortunately, all tyrosine kinase inhibitors come with side effects. Tyrosine kinase inhibitor bosutinib is on the market, but in contrast to imatinib, only as a second line treatment option. Additional data about safety and tolerability are needed for bosutinib before it may be considered as a first line treatment option. From previous studies it is known bosutinib has a partially different mode of action and also a distinct safety profile, i.e. partially other side effects than Imatinib and other tyrosine kinase inhibitors. Hence, bosutinib may be a suitable alternative for subjects that do not tolerate other tyrosine kinase inhibitors and/or in which other tyrosine kinase inhibitors are not effective. For bosutinib side effects reported include diarrhoea, elevated liver enzymes and

QTc prolongation. Therefore, subjects with chronic intestinal disease, liver disease or taking other medication that prolong QTc have been excluded. Moreover, ECG assessments and diarrhoea management guidelines are part of this study. In addition, from a previous study it is known that a reduction in dose from 500mg/day to 400mg/day reduces side effects significantly, while the efficacy remains favourable. To confirm this observation in the present study, the starting dose for bosutinib in this study is lowered to 400mg/day compared to the standard of care start dose of 500mg/day. Moreover, in the present study, depending on the efficacy and side effects the dose may be adjusted stepwise (reduced and increase dosing). Other side effects of bosutinib and imatinib have been described in question E9. Other risks for subjects in this study comprise of minimal extra exposure to radiation (chest x-ray and MUGA tracer) and pain from additional venepuncture and bone marrow aspirate taken. Benefits for participants could be, but are not guaranteed to be, less side effects in the bosutinib arm due to diarrhoea management guidelines, the lower dosing and optional conditional dosing reduction. Patients on bosutinib showed a shorter time to major molecular respons and complete cytogenic respons. Also closer follow up of patients than in standard of care situation and the possible first-line treatment with bosutinib may or may not be beneficial to subjects participating and future subjects to be treated for CML disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Molecular diagnosis of CP CML of * 6 months (from initial diagnosis).
* Diagnosis of CP CML with molecular confirmation by detection of BCR-ABL rearrangement at screening (cytogenetic assessment for Philadelphia chromosome is not required for enrollment); diagnosis of CP CML will be defined as all of the following per ELN criteria:
a) <15% blasts in peripheral blood and bone marrow;
b) <30% blasts plus promyelocytes in peripheral blood and bone marrow;
c) <20% basophils in peripheral blood;
d) *100 x 109/L platelets (*100,000/mm3);
e) No evidence of extramedullary disease except hepatosplenomegaly; AND
f) No prior diagnosis of AP or BP-CML.
* Philadelphia chromosome status will be identified at screening. Both Ph+ and Ph- patients may be included.
2. Adequate hepatic and renal function defined as:
* AST/ALT *2.5 x upper limit of normal (ULN) or *5 x ULN if attributable to liver involvement of leukemia.
* Total bilirubin *2.0 x ULN (unless associated with Gilbert*s syndrome).
* Creatinine *1.5 x ULN.
3. Able to take oral tablets.
4. ECOG performance status of 0 or 1.
5. Age *18 years.
6. Negative serum pregnancy test within 2 weeks of the first dose of study drug if the patient is a woman of childbearing potential. A woman of childbearing potential is defined as a woman who is biologically capable of becoming pregnant. This includes women who are using contraceptives or whose sexual partners are either sterile or using contraceptives. Patients and patient's partners of childbearing potential (physically able to have children) and who are sexually active, must agree to use double barrier contraception, oral contraceptives, intra-unterine device, intra muscular contraceptive, vasectomy/surgical sterilization, true abstinence or other approved method of birth control consistentlyand correctly during the study and for at least 28 days after they have stopped taking the study drug.
7. Ability to provide written informed consent prior to any study related screening procedures being performed.

Exclusion criteria

1. Any prior medical treatment for CML, including TKIs, with the exception of hydroxyurea

and/or anagrelide treatment which are permitted up to 6 months prior to study entry (signature of ICF)
2. Any past or current CNS involvement, including leptomeningeal leukemia.
3. Hypersensitivity to the active substance or to any of the following excipients: microcrystalline cellulose (E460), croscarmellose sodium (E468), poloxamer 188, povidone (E1201), magnesium stearate (E470b), polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, Talc (E553b), iron oxide yellow (E172).
4. Extramedullary disease only.
5. Major surgery or radiotherapy within 14 days of randomization.
6. Concomitant use of or need for medications known to prolong the QT interval.
7. History of clinically significant or uncontrolled cardiac disease including:
* History of, or active, congestive heart failure.
* Uncontrolled angina or hypertension within 3 months.
* Myocardial infarction (within 12 months).
* Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes).
* Diagnosed or suspected congenital or acquired prolonged QT history or prolonged QTc (QTcF should not exceed 500 msec).
* Unexplained syncope.
8. Known seropositivity to human immunodeficiency virus (HIV), current acute or chronic hepatitis B (hepatitis B surface-antigen positive), hepatitis C or evidence of decompensated liver disease or cirrhosis. Patients with resolved Hepatitis B can be included.
9. Recent or ongoing clinically significant GI disorder, e.g. Crohn*s Disease, Ulcerative Colitis, or prior total or partial gastrectomy.
10. History of another malignancy within 5 years with the exception of basal cell carcinoma or cervical carcinoma in situ or stage 1 or 2 cancer that is considered adequately treated and currently in complete remission for at least l2 months.
11. Uncontrolled hypomagnesemia or uncorrected hypokalemia due to potential effects on the QT interval.
12. Current, or recent (within 30 days, or 5 half-lives of investigational product), participation in other clinical trials of investigational agents and/ or containing interventional procedures deemed contrary to the objectives and conduct of this trial.
13. Women who are pregnant, planning to become pregnant during the study or are breastfeeding a child, or men who are planning to father a child during the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-11-2014
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bosulif
Generic name:	Bosutinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Glivec/Gleevec
Generic name:	Imatinib mesylate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-10-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-12-2019
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
EudraCT	EUCTR2013-005101-31-NL
CCMO	NL48355.029.14

Study results

Results posted: 11-02-2021

First publication
07-10-2020