A phase I, multicenter, open-label study of oral ABL001 in patients with chronic myelogenous leukemia or Philadelphia Chromosome-positive acute lymphoblastic Leukemia (CABL001X2101)

Published: 20-02-2014
Last updated: 20-04-2024

Primary:Determine the MTD and/or RDE(s) of ABL001:* As a single agent for CML CP and AP patients* In combination with either nilotinib or imatinib or dasatinib in CML CP and AP patients* As a single agent for CML BP patients and Ph+ ALL...

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

Summary

ID

NL-OMON55523

Source
ToetsingOnline

Brief title
CABL001X2101

Condition

- Leukaemias

Synonym
leukemia; chronic myelogenous leukemia/Philadelphia chromosome-positive acute lymphoblastic leukemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ABL001, ALL, CML, leukemia

Outcome measures

Primary outcome

Number of dose limiting toxicities.

Secondary outcome

Main efficacy endpoint : MMR rate by 24 weeks of treatment

Secondary efficacy endpoints : Hematologic, cytogenic, molecular response,

plasma concentration, changes in pSTAT5 and pCRKL, adverse effects.

Study description

Background summary

Despite the dramatic progress made over the past decade with TKIs in the treatment of Chronic Myeloid Leukemia (CML), allogeneic stem cell transplant remains the only proven curative therapy. To achieve cure or benefit from treatment-free remissions with pharmacologically-based therapies, it is estimated that patients will likely need to achieve a sustained reduction in tumor burden of at least 4 logs, often referred to as a complete molecular response (CMR). Currently, only 32% and 11% of patients achieve CMR after 12 months of treatment with single agent nilotinib or imatinib, respectively.
The development of the novel and potent BCR-ABL (Breakpoint Cluster Region-Abelson oncogene) allosteric inhibitor, ABL001, presents an opportunity to assess the effect of a different mechanism of inhibition of BCR-ABL in the treatment of CML and Ph+ ALL (Philadelphia Chromosome-positive acute lymphoblastic Leukemia).
This first-in-human trial with ABL001 is a dose escalation study whose primary purpose is to estimate the maximum tolerated dose (MTD) and/or recommended dose for expansion of ABL001 administered orally as a single agent to adult patients with CML or Ph+ ALL.

By virtue of its distinct pharmacological profile and by preclinical pharmacological studies demonstrating an additive effect, a combination of ABL001 and a Tyrosine Kinase Inhibitor (TKI) has the potential to achieve a deeper molecular response in a higher proportion of CML patients as compared to single agent TKI therapy. Such a combination has the added theoretical advantage of preventing treatment resistance. The prediction is that a TKI/ABL001 combination will increase the percentage of patients who achieve a CMR and decrease the time to CMR. In addition, some patients may be intolerant of therapy with TKIs or may develop mutations that promote resistance to TKI therapy. In these patients, ABL001 may provide a novel therapeutic option.

Study objective

Primary:Determine the MTD and/or RDE(s) of ABL001:
* As a single agent for CML CP and AP patients
* In combination with either nilotinib or imatinib or dasatinib in CML CP and AP patients
* As a single agent for CML BP patients and Ph+ ALL patients
Secondary: Characterize the safety and tolerability of oral ABL001 as a single agent and in combination
with either nilotinib or imatinib or dasatinib
* To assess the pharmacokinetic profile of all study drugs in single agent and combination
arms in plasma
* To assess preliminary anti-CML activity associated with ABL001 as a single agent and in
combination with either nilotinib or imatinib or dasatinib and preliminary anti Ph+ ALL activity
associated with ABL001 as a single agent

Study design

There will be 5 arms in this study:
* Arm 1: ABL001 as single agent in CP and AP CML patients including an expansioncohort with approx. 65 patienten with a T315I mutation
* Arm 2: ABL001 in combination with nilotinib in CP and AP CML patients

* Arm 3: ABL001 in combination with imatinib in CP and AP CML patients
* Arm 4: ABL001 in combination with dasatinib in CP and AP CML patients
* Arm 5: ABL001 as single agent in CML blast phase and Ph+ ALL patients
Each arm will begin with a dose escalation part and then have an expansion part. After
determination of each MTD/RDE(s), further safety and tolerability will be evaluated in the
expansion part.

Intervention

Treatment with ABL001 as single agent and in combination with nilotinib, dasatinib en imatinib.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Cycle 1: 6 visits, cycle 2; 5 visits, thereafter: 2 visits per cycle.
Visit duration 3-4 h (2-3 PK visits of 8 h).
Physical examination 2-3 times per cycle.
Blood draws every visit (10-30 ml); during 2-3 serial PK visits 8 samples.
Bone marrow sample at screening. To be repeated if needed.
ECG 1-2 times per cycle (up to cycle 6).
MRI-scan abdomen screening, cycle 2, every 3rd cycle thereafter.

Contacts

Public
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL
Scientific
Novartis

Haaksbergweg 16
Amsterdam 1101 BX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Inclusion criteria

• Male or female patients at least 18 years of age.
• CML in chronic or accelerated phase who were previously treated with two different tyrosine kinase inhibitors prior to study entry and are relapsed, refractory to or intolerant of TKIs as determined by investigators
Or
Philadelphia chromosome-positive ALL and be relapsed or refractory to one prior TKI or intolerant of TKIs.
See protocol page 26-27 for further details.
• ECOG performance status 0-2.

Exclusion criteria

• Systemic antineoplastic therapy or any experimental therapy within 14 days or 5 half-lives, whichever is longer, before the first dose of ABL001
For patients receiving ABL001 in combination with either nilotinib, or imatinib or dasatinib, intolerance to nilotinib, imatinib or dasatinib, respectively
• Radiotherapy within 1-4 weeks of the first dose of ABL001. See protocol page 27 for details.
• CNS irradiation for meningeal leukemia, except if radiotherapy occurred > 3 months previously.
• Clinical laboratory results: see protocol page 27-28.
• Active infection.
• History of significant bleeding disorder unrelated to cancer.
• History of acute pancreatitis within 1 year of study entry, chronic pancreatitis, or any ongoing pancreatic disease not considered related to the malignancies under study.
• Pregnant or lactating women.
• Women of child-bearing potential using inadequate contraception. See protocol page 28-29 for details.
• Males in arm 4 must use a condom during intercourse while taking the drug and for 30 days after stopping treatment and should not father a child in this period.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-11-2015
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ABL001
Generic name:	ABL001
Product type:	Medicine
Brand name:	Gleevec
Generic name:	Imatinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sprycel
Generic name:	Dasatinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tasigna
Generic name:	nilotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-02-2014

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2016

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2022
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	EUCTR2013-004491-36-NL
CCMO	NL47519.029.14