Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL)

Published: 12-07-2016
Last updated: 25-03-2025

The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL).

Ethical review	Approved WMO
Status	Completed
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON55465

Source
ToetsingOnline

Brief title
M15-550

Condition

- Leukaemias

Synonym
Leukemia; Cancer of the blood

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: AbbVie

Intervention

Keyword: 17p deletion, ABT-199/ Venetoclax, CLL, TP53 mutation

Outcome measures

Primary outcome

The primary efficacy endpoint will be measured by complete remission rate (CR + CRi) of the subjects who have not been previously treated with BCRi therapy as assessed by the investigator.

Secondary outcome

Key secondary efficacy endpoints:

Overall response rate, duration of response, time to progression, progression-free survival, overall survival, complete remission rate in B-cel receptor inhibitor treated subjects.

Study description

Background summary

Chronic lymphocytic leukemia is a lymphoproliferative disorder, characterized by progressive accumulation of B cells in peripheral blood, bone marrow, and secondary lymphoid organs. It is the most common form of leukemia in adults in the Western World, accounting for approximately 30% of all leukemias. The approximate 5-year survival rate for patients with CLL is 73%. Standard chemotherapeutic options for CLL cause significant immune suppression, are not well-tolerated by the elderly population and have not consistently offered survival advantage. With the notable exception of allogeneic stem cell transplantation, CLL is currently an incurable disease, despite good initial responses to chemo immunotherapy.

Despite some improvement in disease outcomes in relapsed/refractory CLL subjects, including those who have received novel agents, significant toxicities remain a concern, complete disease responses are uncommon, and relapse is virtually inevitable.
Current treatment recommendations for patients carrying TP53 aberrations and those who have failed or are intolerant to a BCRi include participation in investigative clinical trials proceeding to allogeneic hematopoietic stem cell transplantation. Globally, access to allogeneic stem cell transplant and/or clinical trials is limited, and treatment options for relapsed disease tend to have increased toxicity and reduced antitumor activity. This group continues to represent a significant unmet medical need.

Venetoclax, also known as ABT-199, is a novel, orally available, small molecule Bcl-2 family protein inhibitor that binds with high affinity to Bcl-2.
Selective inhibition by venetoclax disrupts Bcl-2 signaling and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent human tumor cell lines, independent of p53 activity.
There is data that shows substantial efficacy of venetoclax monotherapy in the treatment of relapsed/refractory CLL characterized by 17p deletions. Venetoclax is expected to be as active in subject selected for TP53 mutations as these subject populations overlap and the oncogenic effect of both genetic defects occurs via p53 abrogation. In addition, there is limited data in the BCRi failure CLL population for subjects that subsequently receive venetoclax.
Clinical safety data indicate that the adverse effects of venetoclax administered with appropriate measures are manageable and as expected from a treatment targeting hematologic cells including in patients with 17p, TP53 mutation or BCRi failure patients.

This study will further investigate the efficacy of venetoclax monotheraphy in subject with relapsed/ refractory CLL.

Study objective

The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL).

Study design

An Open-Label, Single Arm, Phase 3b, Multi-Center Study.

Intervention

Subjects receive venetoclax orally once daily. During the 5 week dose titration the initial dose of venetoclax 20 mg QD will be escalated every week until the maximum dose of 400 mg QD is reached (week 1: 20 mg, week 2: 50 mg, week 3: 100

mg, week 4: 200 mg, week 5: 400 mg). In this period subjects will visit the site on days 1 and 2 of every week. From week 8 on subjects will visit every 4 weeks until week 48. Thereafter, subjects will visit once every 12 weeks up to the final visit in week 108.

Study burden and risks

The subjects participating in the study will have a higher burden because of participation in the trial. This burden consists of extra visits to the site, two times a CT scan, additional blood draws besides the standard safety labs. Next to this, the subjects will complete 3 questionnaires (EQ-5D-5L, FACT-Leu en FACIT-F) during 11 visits and the subjects will be asked to keep a medication diary. While being treated with venetoclax subjects are not allowed to consume any grapefruit or Sevilla oranges or starfruit. Also the products related to these fruits (including marmalade which contains Sevilla oranges) are not allowed.

Subjects will daily take venetoclax orally. Possible adverse events include: nausea, vomiting, diarrhea, constipation, feeling tired, decreases in lymphocytes and neutrophils (two different types of white blood cells), decreases in red blood cells, tumor lysis syndrome (TLS) and infections. Some common infections were pneumonia (infection of the lungs) and infections of the nose and throat and urinary organs.

Before the start of treatment subjects will be classified based on the risk to develop TLS. When necessary due to a high risk to develop TLS subjects can be hospitalized during the dose titration phase for observation (1 or 2 days).

The current data of venetoclax and the lack of a curative treatment alternative reflect an acceptable rationale and risk for treating adult patients with relapsed or refractory CLL with venetoclax in the context of a clinical trial.

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. Age >= 18 years., 2. Eastern Cooperative Oncology Group (ECOG) performance score of <= 2., 3. Subject has relapsed/refractory disease (received at least one line of prior therapy). , 4. Diagnosis of CLL that meets published 2008 Modified International Workshop on CLL National Cancer Institute - Working Group (IWCLL NCI-WG) Guidelines and:
• has an indication for treatment according to the 2008 Modified IWCLL NCI-WG Guidelines
• has clinically measurable disease (lymphocytosis > 5 × 10^9/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam)
• subjects with or without the 17p deletion or TP53 mutation are eligible
• subjects who have received prior B-cell receptor inhibitor therapy are also eligible (up to 60 subjects total will be enrolled in the study), 5. Adequate bone marrow function as follows:
• platelets >= 25,000/mm^3 without any of the following:
o transfusion support within 14 days of Screening
o evidence of mucosal bleeding
o known history of bleeding episode within 3 months of Screening
• hemoglobin >= 8.0 g/dL

Exclusion criteria

1. Subject has developed Richter's transformation or Prolymphocytic leukemia (PLL), 2. Subject has previously received venetoclax., 3. History of active

malignancies other than CLL within the past 2 years prior to first dose of venetoclax, with the exception of:
• adequately treated in situ carcinoma of the cervix uteri
• adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin
• previous malignancy confined and surgically resected (or treated with other modalities) with curative intent., 4. Active and uncontrolled autoimmune cytopenias (within 2 weeks prior to Screening), including autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), despite low dose corticosteroids., 5. Prior allogeneic stem cell transplant.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-03-2017
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Venetoclax
Generic name:	Venetoclax

Ethics review

Approved WMO

Date:	12-07-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date: 21-07-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 01-09-2017

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 29-03-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 11-04-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 26-09-2018

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 03-01-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 28-01-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 11-03-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 12-03-2019

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date:	31-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	22-03-2022
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	EUCTR2015-003667-11-NL
ClinicalTrials.gov	NCT02756611
CCMO	NL56737.018.16

Study results

Date completed:	17-03-2022
Results posted:	06-04-2023

First publication
20-02-2023

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File