A Randomized, Open-label, Phase 3 study of the Combination of Ibrutinib plus Venetoclax versus Chlorambucil plus Obinutuzumab for the First-line Treatment of Subjects with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

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This study has been transitioned to CTIS with ID 2023-503469-49-00 check the CTIS register for the current data. Primary ObjectiveThe primary objective of the study is to assess progression-free survival (PFS) from treatment with ibrutinib plus...

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

Summary

ID

NL-OMON54563

Source
ToetsingOnline

Brief title
54179060CLL3011 / GLOW

Condition

- Leukaemias

Synonym
Chronic Lymphocytic Leukemia /Small Lymphocytic Lymphoma - CLL/SLL

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Door de verrichter.

Intervention

Keyword: CLL/ SL, First-line treatments, Ibrutinib, Venetoclax

Outcome measures

Primary outcome

Efficacy evaluations will include imaging, physical examinations, evaluation of blood and bone marrow, disease-related symptoms, and assessment of patient-reported outcomes (PRO). Safety evaluations will include adverse event (AE) monitoring, physical examinations, laboratory tests, and review of concomitant medications.

Secondary outcome

To better understand the molecular and protein markers associated with response to and relapse following study treatment, bone marrow and peripheral blood samples will be collected. For subjects assigned to the I+VEN treatment arm, sparse samples will be collected for pharmacokinetic (PK) analysis.

Study description

Background summary

Refer to question answer C4.
Hypothesis:
Treatment with the combination of I+VEN will result in longer PFS compared with G-Clb in subjects with previously untreated chronic lymphocytic leukemia (CLL)/

small lymphocytic lymphoma (SLL).

Study objective

This study has been transitioned to CTIS with ID 2023-503469-49-00 check the CTIS register for the current data.

Primary Objective
The primary objective of the study is to assess progression-free survival (PFS) from treatment with ibrutinib plus venetoclax (I+VEN) compared with obinutuzumab plus chlorambucil (G-Clb) as assessed by an Independent Review Committee (IRC).
Secondary Objectives
Key secondary objectives are to evaluate the following: rate of minimal residual disease (MRD)-negative remissions; overall response rate (ORR), including complete response (CR) rate, and response duration as assessed by an IRC; overall survival (OS); time-to-next treatment; trough levels of ibrutinib when given in combination with venetoclax; and safety.

Study design

This is a randomized (1:1), open-label, multicenter, Phase 3 study to determine the efficacy and safety of the combination of I+VEN, compared with G-Clb, in approximately 200 subjects with previously untreated CLL/SLL who meet the International Workshop on CLL (iwCLL) treatment criteria.
Randomization will be stratified by immunoglobulin heavy-chain variable region (IGHV) gene mutational status (mutated vs. unmutated vs. not available) and presence of deletion of the long arm of chromosome 11 ([del11q] yes vs. no).

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. After treatment completion, subjects will enter a Follow-up Phase, and those without progression will continue disease evaluations until disease progression or death. Study end is defined as approximately 5 years after the last subject is randomized into the study or after 50% of subjects have died, whichever occurs first.

If the disease worsens after receiving Treatment Group A or Treatment Group B and further treatment is required, the subject might be eligible to receive further treatment with only ibrutinib. The purpose of this part of the study is to look at the effectiveness in patients who were initially treated with Treatment Group A (combination of ibrutinib and venetoclax). If the subject was receiving Treatment Group B (obinutuzumab in combination with chlorambucil) the subject may also be eligible to receive this further treatment with only ibrutinib. Ibrutinib alone is an approved second line therapy for subjects whose CLL/SLL worsens after prior treatments or therapy.

Intervention

Subjects randomly assigned to Arm A (I+VEN) will receive ibrutinib (420 mg/day orally) given as leadin treatment for 3 cycles. Starting at Cycle 4, venetoclax dose ramp up (from 20 mg to 400 mg over 5 weeks) will begin, and venetoclax will be administered with ibrutinib for 12 cycles. Subjects randomly assigned to Arm B (G-Clb) will receive G-Clb for 6 cycles. Obinutuzumab will be administered intravenously at a dose of 1000 mg on Days 1, 8 and 15 in Cycle 1. In Cycles 2 to 6, 1000 mg obinutuzumab will be given on Day 1. Chlorambucil will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of Cycles 1 to 6. A cycle will be defined as 28 days.
If the subject was receiving Treatment Group B (obinutuzumab in combination with chlorambucil) the subject may also be eligible to receive this further treatment with only ibrutinib. Ibrutinib alone is an approved second line therapy for subjects whose CLL/SLL worsens after prior treatments or therapy.

Study burden and risks

Burden (both arm A and B): hospital visits on a more frequent schedule than standard, including additional assessments like questionnaires and CT-scans.
Risks: Adverse events from Ibrutinib, Venetoclax, Chlorambucil and Obinutuzumab: see informed consent, SmPC and IB. Side effects from bloodtests and bone marrow biopsy and bone marrow aspirate.

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. Adult subjects who are: , a. >=65 years old or, , b. 18 to 64 years old and have at least 1 of the following:, - Cumulative Illness Rating Scale (CIRS) score >6, - Creatinine clearance (CrCl) estimated <70 mL/min using the Cockcroft-Gault equation., 2. Diagnosis of CLL or SLL that meets iwCLL criteria. , 3. Active CLL/SLL requiring treatment per the iwCLL criteria: , a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia or thrombocytopenia or both;, b. Massive (ie, at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly;, c. Massive nodes (ie, at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy;, d. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time of less than six months;, e. Constitutional symptoms, defined as 1 or more of the following:, - Unintentional weight loss >=10% within the previous 6 months prior to the start of screening;, - Significant fatigue (inability to work or perform usual activities);, - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without evidence of infection; , - Night sweats for more than 1 month without evidence of infection., 4. Measurable nodal disease (by computed tomography [CT]) is defined as at least one lymph node >;1.5 cm in longest diameter. , 5. ECOG Performance Status Grade <=2., 6. Adequate organ function defined as follows:, a. Absolute neutrophil count (ANC) >=750 cells/µL independent of growth factor support;, b. Platelets >=50,000 cells/µL independent of transfusion support for at least 7 days prior to randomization;, c. Hemoglobin >8.0 g/dL independent of transfusion support for at least 7 days prior to randomization;, d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=3.0 x upper limit of normal (ULN);, e. Total bilirubin <=1.5 x ULN (unless due to Gilbert*s syndrome);, f. Estimated CrCl >=30 mL/min (Cockcroft-Gault equation).

Exclusion criteria

1. Prior anti-leukemic therapy for CLL or SLL., 2. Presence of del17p or known

TP53 mutation., 3. Major surgery within 4 weeks of first dose of study treatment. , 4. Known bleeding disorders (eg, von Willebrand*s disease or hemophilia)., 5. Central nervous system (CNS) involvement or suspected Richter*s syndrome., 6. An individual organ/system impairment score of 4 as assessed by CIRS, except for the eyes, ears, nose, throat, and larynx system, limiting the ability to receive treatment in this study., 7. Uncontrolled autoimmune hemolytic anemia or autoimmune thrombocytopenia (Coombs positivity in the absence of hemolysis is not an exclusion)., 8. Chronic use of corticosteroids more than 20 mg/day of prednisone or its equivalent within 7 days of initiation of study treatment., 9. History of prior malignancy, except:, a. Malignancy treated with curative intent and with no known active disease present for >=24 months before randomization;, b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease;, c. Adequately treated cervical carcinoma in situ without evidence of disease;, d. Malignancy, which is considered cured with minimal risk of recurrence., 10. Received live, attenuated vaccine within 4 weeks of randomization., 11. History of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, or hepatic condition that in the opinion of the investigator would adversely affect a subject*s participation in the study., 12. Currently active, clinically significant Child-Pugh Class B or C hepatic impairment according to the Child Pugh classification (see Attachment 4 Child-Pugh classification), 13. Uncontrolled active systemic infection or any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator*s opinion, could compromise the subject*s safety or put the study outcomes at undue risk., 14. Inability or difficulty swallowing capsules/tablets, malabsorption syndrome, or any disease or medical condition significantly affecting gastrointestinal function.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-05-2018
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gazyvaro
Generic name:	Obinutuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Imbruvica
Generic name:	Ibrutinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Leukeran
Generic name:	Chlorambucil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Venclyxto
Generic name:	Venetoclax
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-02-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-05-2018
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2018
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:	12-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2023
Application type:	Amendment
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Approved WMO Date:	21-02-2023
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Approved WMO Date:	30-08-2023
Application type:	Amendment
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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
EU-CTR	CTIS2023-503469-49-00
EudraCT	EUCTR2017-004699-77-NL
CCMO	NL64467.018.18