A study investigating the effect of adding revumenib to treatment with venetoclax + azacitidine in patients with acute myeloid leukemia (AML) with a specific gene abnormality and who have not been treated before and who are not eligible for intensive chemotherapy.

Estado	Tipo de Participantes	Rangos de Edad
Reclutando	No aportado	Mayores de 64 , Adultos (18-64 años)
Género	**Fases**	**Participantes esperados**
Ambos	Fase III	448
Resultados	**Bajo nivel intervención**	**Enfermedad rara**
Sin resultados	No	No
Cobertura geográfica	**Ámbitos del ensayo**	**Terapia avanzada**
Multicéntrico internacional	tratamiento, seguridad, eficacia, farmacocinética	NO

Información

Identificador
2024-512733-32-00 (CTIS)

Cod. Protocolo
HOVON-177 AML

Área terapéutica
Enfermedades [C] - Cáncer [C04]|

Enfermedad investigada
Acute Myeloid Leukemia (AML)

Título Científico
HOVON 177: Randomized study to assess revumenib in combination with azacitidine + venetoclax in adult patients with newly diagnosed NPM1 mutated or KMT2A rearranged AML ineligible for intensive chemotherapy

Justificación

No aportado

Objetivo Principal

To assess if treatment with revumenib, in combination with azacitidine and venetoclax, improves overall survival (OS) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the combined rate of complete remission (CR) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.

Variables de Evaluación Primaria

OS in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, measured from the date of randomization to the date of death from any cause; Rate of CR in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients who achieve CR at any time-point during protocol therapy.

Momentos temporales de evaluación primaria

No aportado

Objetivo Secundario

To assess if treatment with revumenib, in combination with azacitidine and venetoclax, prolongs event-free survival (EFS) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CRMRD-, CR/CRhMRD- and CR/CRiMRD- assessed by quantitative PCR of peripheral blood in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CR in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CRh in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the combined rate of CR and CR with incomplete hematologic recovery (CRi) (CR/CRi) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CR, CR/CRh and CR/CRi without measurable residual disease (CRMRD-, CR/CRhMRD- and CR/CRiMRD-) assessed by quantitative PCR in bone marrow in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, shortens the time to response (CR, CR/CRh and CR/CRi) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, prolongs duration of response (CR, CR/CRh and CR/CRi; DoR) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.

To evaluate OS, CR rate, EFS, rates of CR/CRh, CR/CRi and DoR by prognostic variables, including clinical variables (e.g., age at randomization, sex, ECOG performance status, white blood cell count), 2022 European LeukemiaNet (ELN) risk groups, geographical region and by specific AML genotypes in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CRMRD-, CR/CRhMRD- and CR/CRiMRD- assessed by multiparameter flowcytometry of bone marrow in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To evaluate resistance mechanisms after combined treatment with azacitidine/venetoclax/revumenib (e.g. MEN1 mutations, RAS mutations, FLT3 mutations, TP53 mutations).
To evaluate the impact of revumenib, in combination with azacitidine and venetoclax, on quality of life (QoL), using EORTC QLQ-C30 and EQ-5D-5 in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To evaluate OS, CR rate, EFS, rates of CR/CRh, CR/CRi, CRMRD-, CR/CRhMRD-, CR/CRiMRD, time to response, DoR and QoL in adult patients with newly diagnosed KMT2A-rearranged AML ineligible for intensive chemotherapy.
To characterize PK parameters and assess the exposure-response relationships of revumenib and primary metabolite in combination with azacitidine and venetoclax.
To evaluate revumenib pharmacodynamic relationship with safety, efficacy and correlative biomarkers, which may include immunophenotyping of circulating peripheral blood mononuclear cells (PBMC) and/or bone marrow, gene expression, mutational analysis, and minimal residual disease (MRD).
To evaluate the incidence and severity of adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version v5.0.
To assess time to hematopoietic recovery (absolute neutrophil counts [ANC] 0.5 and 1.0 x 109/L; platelet counts 50 and 100 x 109/L) after each cycle (but at least for each of the first 6 cycles).
To assess the need for blood transfusions (platelet and RBC) and the lenght of hospital stay.

Variables de Evaluación Secundaria

EFS in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, measured from the date of randomization to the date of treatment failure, hematologic relapse from CR/CRh or death from any cause, whichever occurs first. Treatment failure is defined as lack of obtaining either CR or CRh by week 24
Rate of CR/CRh in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients who achieve CR or CRh at any time-point during protocol therapy.
Rate of response (CRh and CR/CRi) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients with response at any time-point during protocol therapy.
Rates of CRMRD-, CR/CRhMRD- and CR/CRiMRD- assessed by quantitative PCR of bone marrow in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients with CRMRD-, CR/CRhMRD- and CR/CRiMRD- by PCR in bone marrow, respectively, at any time-point during protocol therapy.
Time to achievement of response (CR, CR/CRh and CR/CRi) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as time from the date of randomization to until the 1st occurrence of the response.
Duration of response (CR, CR/CRh and CR/CRi; DoR) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, measured from the date of achievement of response until the date of hematologic relapse or death from any cause; patients without any of these events will be censored on the date of the last clinical assessment.
OS, CR rate, EFS, rates of CR, CR/CRh, CR/CRi, and DoR across different patient subgroups in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, where the groups are defined based on prognostic variables including clinical variables (e.g., age at randomization, sex, ECOG performance status, white blood cell count), risk category, geographical region as well as specific AML genotypes.
Rates of CRMRD, CR/CRhMRD- and CR/CRiMRD- assessed by multiparameter flowcytometry of bone marrow at any time-point during protocol therapy in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients with CRMRD-, CR/CRhMRD- and

CR/CRiMRD- by multiparameter flowcytometry, respectively, at any time-point during protocol therapy.
Resistance mechanisms after combined treatment with azacitidine/venetoclax/revumenib (e.g. MEN1 mutations, RAS mutations, TP53 mutations, FLT3 mutations).
Quality of life (QoL) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy as assessed by EORTC QLC-C30 and EQ-5D-5L questionnaires.
OS, CR rate, EFS, rates of CR/CRh, CR/CRi, CRMRD-, CR/CRhMRD-, CR/CRiMRD-, time to response, DoR and QoL as assessed by EORTC QLQ-C30 and EQ-5D-5L questionnairesas defined above in adult patients with newly diagnosed KMT2A-rearranged AML ineligible for intensive chemotherapy.
Descriptive summary of plasma concentrations and PK parameters of revumenib and the primary metabolites.
Descriptive summary of revumenib pharmacodynamics in relation to safety, efficacy and correlative biomarkers, which may include immunophenotyping of circulating peripheral blood mononuclear cells (PBMC) and/or bone marrow, gene expression, mutational analysis, and minimal residual disease (MRD).
Frequency and severity of AE according to CTCAE version 5.0.
Time to hematopoietic recovery (absolute neutrophil counts 0.5 and 1.0 x 109/L; platelets 50 and 100 x 109/L) after each treatment cycle (but at least for each of the first 6 cycles), defined as the time from the start of the cycle until recovery.
Number of patients requiring transfusions (platelet and RBC) and number of units transfused, rate and duration of transfusion independence, length of hospital stay, where transfusion independence is defined as a period of at least 56 days with no transfusion between the first dose of study drug and the last dose of study drug + 30 days.
Rates of CRMRD-, CR/CRhMRD-, and CR/CRiMRD- assessed by quantitative PCR of peripheral blood in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients with CRMRD-, CR/CRhMRD- and CR/CRiMRD- by PCR in peripheral blood, respectively, at any time-point during protocol therapy.

Momentos temporales de evaluación secundaria

No aportado

Criterios de Inclusión

Patient with newly diagnosed NPM1-mutated AML, consistent with NPM1c, according to the 2022 International Consensus Classification (i.e. 10% blasts). OR Patient with newly diagnosed KMT2A-rearranged AML according to the 2022 International Consensus Classification (i.e. 10% blasts). KMT2A partial tandem duplications or deletions are NOT eligible. Of note: in case both NPM1 and IDH1 are mutated and both EVOLVE-1 (HO173) and EVOLVE-2 (HO177) are open for inclusion at your site, then patients can only be included in the EVOLVE-1 trial (HO173) Men must use a latex condom during any sexual contact with women of childbearing potential (WOCBP), even if they have undergone a successful vasectomy and must agree to avoid to father a child (while on therapy and for 6 months after the final study drug administration). In addition, their female partners of childbearing potential must use a highly effective method of birth control. Male patient must not donate sperm starting at screening and throughout the study period and for 6 months after the final study drug administration. Able to understand and willing to sign an informed consent form (ICF). Institutional Review Board/Independent Ethics Committee-approved written informed consent as per national regulations must be obtained from the patient prior to any study-related procedures (including consent for withdrawal of prohibited medication, if applicable). Central confirmation of NPM1 mutation or KMT2A rearrangement in one of the dedicated central genetic laboratories. Age 18 years, no upper age limit. Patient is ineligible for intensive induction chemotherapy by meeting at least 1 of the following criteria: 75 years of age: ineligible for intensive chemotherapy per physicians discretion (with an ECOG performance status 0-2) 18-74 years: patient is not eligible for standard chemotherapy because any of the following co-morbidities: ECOG performance status 2 or 3 Cardiac history of chronic heart failure requiring treatment; or with an ejection fraction 50%; or chronic stable angina. DLCO 65% or FEV1 65%. Creatinine clearance 30 mL/min to <45 ml/min calculated by the Cockcroft Gault formula. Moderate hepatic impairment with total bilirubin > 1.5 to < 3.0 x upper limit of normal (ULN). Any other comorbidity that the local physician assesses to be incompatible with intensive chemotherapy. Patient must have a

projected life expectancy of at least 12 weeks (as assessed by the treating physician). Patient must have a white cell blood (WBC) count of < 25 x 109/L. Hydroxyurea can be used prior to study enrollment to reduce the WBC count to meet this criterion. Adequate renal function as evidenced by serum creatinine 2.0 × upper limit of norm (ULN) or creatinine clearance >30 mL/min based on the Cockcroft-Gault glomerular filtration rate (GFR). Adequate hepatic function as evidenced by: Serum total bilirubin 3.0 × ULN unless considered due to Gilberts disease, or leukemic involvement; Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) 3.0 × ULN, unless considered due to leukemic involvement. Female patient must: be of nonchildbearing potential: or, if of childbearing potential (not surgically sterile and not postmenopausal) agree to avoid pregnancy during the study and for 6 months after the final study drug administration; and have a negative urine or serum pregnancy test at screening; and, if heterosexually active, agree to consistently apply one highly effective method of birth control for the duration of the study and for 6 months after the final study drug administration; agree not to breastfeed starting at screening and throughout the study period, and for 1 week after the final study drug administration; agree not to donate ova starting at screening and throughout the study period, and for 6 months after the final study drug administration.

Criterios de Exclusión

Subject has previously been treated for AML; a treatment period with hydroxyurea to control WBC counts is allowed; prior treatment with a hypomethylating agent for MDS-EB is not allowed; prior treatment with erythropoiesis-stimulating agents or luspatercept for MDS is allowed. The patient is a pregnant or lactating woman, or plans to become pregnant during the study. Patient who has once been screened and randomized into this HO177 trial but was considered ineligible cannot re-enter this trial at a later date. Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2); PML-RARA; or one of the other pathognomonic variant chromosomal translocations / fusion genes. AML with BCR-ABL1; or myeloid blast crisis of CML. Significant active cardiac disease within 3 months prior to the start of study treatment, including: New York Heart Association (NYHA) class III or IV congestive heart failure Myocardial infarction Unstable angina Severe cardiac arrhythmias Congenital long QT syndrome of family member with this condition QTcF >450 msec on screening electrogram for males and >470msec on screening electrogram for females (mean of triplicate recordings; calculated using Fridericias correction). Severe obstructive or restrictive ventilation disorder. History of stroke or intracranial hemorrhage within 6 months prior to randomization. Clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid (CSF) during screening is only required if there is a clinical suspicion of CNS involvement by leukemia during screening. Active infection, including hepatitis B or hepatitis C or Human Immunodeficiency Virus (HIV) infection, that is uncontrolled prior to first dose of study treatment and may interfere with the study objectives or which could expose the patient to undue risk through the participation in the clinical trial; an infection controlled with an approved antibiotic/ antiviral/ antifungal treatment that is not a strong or moderate CYP3A inducer is allowed. Immediate life-threatening, severe complications of leukemia such as uncontrolled bleeding and/or disseminated intravascular coagulation. Conditions that limit the ingestion or gastrointestinal absorption of orally administered drugs. Patient weighing <40 kg at registration. Patient with a currently active second malignancy. Patients are not considered to have a currently active malignancy, if they have completed therapy and are considered by their physician to be at < 30% risk of relapse within one year. However, patients with the following history/concurrent conditions are allowed: Basal or squamous cell carcinoma of the skin; Carcinoma in situ of the cervix; Carcinoma in situ of the breast; Incidental histologic finding of prostate cancer. Receipt of live, attenuated vaccine within 30 days prior to the study inclusion (NOTE: patient, if enrolled, should not receive live vaccine during the study and until 6 months after the therapy). Severe neurological or psychiatric disorder interfering with ability to give an informed consent. Contraindication to azacitidine or venetoclax Participation in other prospective studies with anti-leukemic and/or investigational agents. Patient taking Dabigatran unless they can be transferred to other medications within 5 half-lives prior to dosing. Patients taking other P-gP transporter-sensitive medications should be properly monitored during the study if they cannot be transferred to other medications Patients taking known strong cytochrome P450 (CYP) 3A4 inducers, unless they can be transferred to other medications within 5 half-lives prior to dosing.

Calendario

(Última actualización: 26/05/2026)

Autorización	Inicio de Ensayo	Inclusión Primer Paciente	Interrumpido	Reiniciado
06/08/2025	12/12/2025	24/03/2026	No aportado	No aportado

Fin de reclutamiento	Fin prematuro (España)	Fin prematuro (Global)	Fin del ensayo en España	Fin del ensayo global
No aportado	No aportado	No aportado	No aportado	No aportado

Promotor

Hemato-Oncologie voor Volwassenen Nederland (Hovon) Stichting Netherlands

Dr. Molewaterplein 40

Contact Person

HOVON

0031107041560

hovon@erasmusmc.nl

Monetary support: N/A

Tipo de promotor: No comercial

Ceim

CEIm Fundacio de Gestio Sanitaria Hospital de la Santa Creu i Sant Pau

C/ Sant Quintí, 77-79. Planta 1a. Despacho 95 08041 Barcelona

ceimsantpau@santpau.cat

935537813

Centros

Activo (28/01/2026)

Fundacio Assistencial De Mutua De Terrassa Fpc

Terrassa

BARCELONA

Haematology

Activo (23/12/2025)

Hospital Clinic De Barcelona

Barcelona

BARCELONA

Haematology

Activo (16/12/2025)

Hospital Clinico Universitario De Valencia

Valencia

VALENCIA

Haematology

Activo (05/02/2026)

Hospital De La Santa Creu I Sant Pau

Barcelona

BARCELONA

Haematology

Activo (06/03/2026)

Hospital Del Mar

Barcelona

BARCELONA

Haematology

Activo (16/02/2026)

Hospital General Universitario Gregorio Maranon

Madrid

MADRID

Haematology

Activo (12/12/2025)

Hospital Universitari Arnau De Vilanova De La Gerencia Territorial De Lleida

Lleida

LÉRIDA

Haematology

No iniciado (--/--/----)

Hospital Universitari Joan XXIII De Tarragona

Tarragona

TARRAGONA

Haematology

Activo (20/03/2026)

Institut Catala D´oncologia

Girona

GERONA

Haematology

Activo (24/03/2026)

Institut Catala D´oncologia

L'hospitalet De Llobregat

BARCELONA

Haematology

Activo (24/02/2026)

Institut Catala D´oncologia

Badalona

BARCELONA

Haematology

Activo (19/02/2026)

University Hospital Son Espases

Palma

BALEARES

Haematology

Medicamentos

Venclyxto 10 mg film-coated tablets
FILM-COATED TABLET
ORAL

Código ATC: L01XX52 - VENETOCLAX
Principios Activos: N/A

Experimental

Venclyxto 10 mg film-coated tablets
FILM-COATED TABLET
ORAL

Código ATC: L01XX52 - VENETOCLAX
Principios Activos: N/A

Experimental

Revumenib
TABLET
ORAL USE

-
Principios Activos: N/A

Experimental

Revumenib
TABLET
ORAL

-
Principios Activos: N/A

Experimental

Venclyxto 100 mg film-coated tablets
FILM-COATED TABLET
ORAL

Código ATC: L01XX52 - VENETOCLAX
Principios Activos: N/A

Experimental

Revumenib
TABLET
ORAL

-
Principios Activos: N/A

Experimental

Revumenib
TABLET
ORAL

-
Principios Activos: N/A

Experimental

Azacitidine Seacross 25 mg/mL powder for suspension for injection
SUSPENSION FOR INJECTION
SUBCUTANEOUS

Código ATC: L01BC07 - AZACITIDINA
Principios Activos: N/A

Experimental

Venclyxto 100 mg film-coated tablets
FILM-COATED TABLET
ORAL

Código ATC: L01XX52 - VENETOCLAX
Principios Activos: N/A

Experimental

Venclyxto 50 mg film-coated tablets
FILM-COATED TABLET
ORAL

Código ATC: L01XX52 - VENETOCLAX
Principios Activos: N/A

Experimental

Venclyxto 50 mg film-coated tablets
FILM-COATED TABLET
ORAL

Código ATC: L01XX52 - VENETOCLAX
Principios Activos: N/A

Experimental

Azacitidine Seacross 25 mg/mL powder for suspension for injection
SUSPENSION FOR INJECTION
SUBCUTANEOUS

Código ATC: L01BC07 - AZACITIDINA
Principios Activos: N/A

Experimental

Revumenib
TABLET
ORAL USE

-
Principios Activos: N/A

Experimental

Revumenib
TABLET
ORAL

-
Principios Activos: N/A

Experimental

Sin resultados

A study investigating the effect of adding revumenib to treatment with venetoclax + azacitidine in patients with acute myeloid leukemia (AML) with a specific gene abnormality and who have not been treated before and who are not eligible for intensive chemotherapy.

State	Type of participants	Age Ranges
Recruiting	Not provided	Older than 64 , Adults (18-64 years)
Gender	**Phases**	**Expected Participants**
Both	Phase III	448
Results	**Low level of intervention**	**Rare disease**
No results	No	No
Geographic coverage	**Areas of the study**	**Advanced therapy**
International multicenter	treatment, safety, effectiveness, pharmacokinetics	NO

Information

Identifier
2024-512733-32-00 (CTIS)

Protocol Code
HOVON-177 AML

Therapeutic area
Diseases [C] - Cancer [C04]|

Investigated Disease
Acute Myeloid Leukemia (AML)

Scientific Title
HOVON 177: Randomized study to assess revumenib in combination with azacitidine + venetoclax in adult patients with newly diagnosed NPM1 mutated or KMT2A rearranged AML ineligible for intensive chemotherapy

Rationale

Not provided

Main Objective

To assess if treatment with revumenib, in combination with azacitidine and venetoclax, improves overall survival (OS) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the combined rate of complete remission (CR) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.

Primary Endpoints

OS in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, measured from the date of randomization to the date of death from any cause; Rate of CR in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients who achieve CR at any time-point during protocol therapy.

Temporary moments of secondary assessment

Not provided

Secondary Objective

To assess if treatment with revumenib, in combination with azacitidine and venetoclax, prolongs event-free survival (EFS) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CRMRD-, CR/CRhMRD- and CR/CRiMRD- assessed by quantitative PCR of peripheral blood in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CR in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CRh in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the combined rate of CR and CR with incomplete hematologic recovery (CRi) (CR/CRi) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CR, CR/CRh and CR/CRi without measurable residual disease (CRMRD-, CR/CRhMRD- and CR/CRiMRD-) assessed by quantitative PCR in bone marrow in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, shortens the time to response (CR, CR/CRh and CR/CRi) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, prolongs duration of response (CR, CR/CRh and CR/CRi; DoR) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.

To evaluate OS, CR rate, EFS, rates of CR/CRh, CR/CRi and DoR by prognostic variables, including clinical variables (e.g., age at randomization, sex, ECOG performance status, white blood cell count), 2022 European LeukemiaNet (ELN) risk groups, geographical region and by specific AML genotypes in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To assess if treatment with revumenib, in combination with azacitidine and venetoclax, increases the rate of CRMRD-, CR/CRhMRD- and CR/CRiMRD- assessed by multiparameter flowcytometry of bone marrow in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To evaluate resistance mechanisms after combined treatment with azacitidine/venetoclax/revumenib (e.g. MEN1 mutations, RAS mutations, FLT3 mutations, TP53 mutations).
To evaluate the impact of revumenib, in combination with azacitidine and venetoclax, on quality of life (QoL), using EORTC QLQ-C30 and EQ-5D-5 in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy.
To evaluate OS, CR rate, EFS, rates of CR/CRh, CR/CRi, CRMRD-, CR/CRhMRD-, CR/CRiMRD, time to response, DoR and QoL in adult patients with newly diagnosed KMT2A-rearranged AML ineligible for intensive chemotherapy.
To characterize PK parameters and assess the exposure-response relationships of revumenib and primary metabolite in combination with azacitidine and venetoclax.
To evaluate revumenib pharmacodynamic relationship with safety, efficacy and correlative biomarkers, which may include immunophenotyping of circulating peripheral blood mononuclear cells (PBMC) and/or bone marrow, gene expression, mutational analysis, and minimal residual disease (MRD).
To evaluate the incidence and severity of adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version v5.0.
To assess time to hematopoietic recovery (absolute neutrophil counts [ANC] 0.5 and 1.0 x 109/L; platelet counts 50 and 100 x 109/L) after each cycle (but at least for each of the first 6 cycles).
To assess the need for blood transfusions (platelet and RBC) and the lenght of hospital stay.

Secondary Endpoints

EFS in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, measured from the date of randomization to the date of treatment failure, hematologic relapse from CR/CRh or death from any cause, whichever occurs first. Treatment failure is defined as lack of obtaining either CR or CRh by week 24
Rate of CR/CRh in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients who achieve CR or CRh at any time-point during protocol therapy.
Rate of response (CRh and CR/CRi) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients with response at any time-point during protocol therapy.
Rates of CRMRD-, CR/CRhMRD- and CR/CRiMRD- assessed by quantitative PCR of bone marrow in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients with CRMRD-, CR/CRhMRD- and CR/CRiMRD- by PCR in bone marrow, respectively, at any time-point during protocol therapy.
Time to achievement of response (CR, CR/CRh and CR/CRi) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as time from the date of randomization to until the 1st occurrence of the response.
Duration of response (CR, CR/CRh and CR/CRi; DoR) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, measured from the date of achievement of response until the date of hematologic relapse or death from any cause; patients without any of these events will be censored on the date of the last clinical assessment.
OS, CR rate, EFS, rates of CR, CR/CRh, CR/CRi, and DoR across different patient subgroups in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, where the groups are defined based on prognostic variables including clinical variables (e.g., age at randomization, sex, ECOG performance status, white blood cell count), risk category, geographical region as well as specific AML genotypes.
Rates of CRMRD, CR/CRhMRD- and CR/CRiMRD- assessed by multiparameter flowcytometry of bone marrow at any time-point during protocol therapy in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients with CRMRD-, CR/CRhMRD- and

CR/CRiMRD- by multiparameter flowcytometry, respectively, at any time-point during protocol therapy.
Resistance mechanisms after combined treatment with azacitidine/venetoclax/revumenib (e.g. MEN1 mutations, RAS mutations, TP53 mutations, FLT3 mutations).
Quality of life (QoL) in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy as assessed by EORTC QLC-C30 and EQ-5D-5L questionnaires.
OS, CR rate, EFS, rates of CR/CRh, CR/CRi, CRMRD-, CR/CRhMRD-, CR/CRiMRD-, time to response, DoR and QoL as assessed by EORTC QLQ-C30 and EQ-5D-5L questionnairesas defined above in adult patients with newly diagnosed KMT2A-rearranged AML ineligible for intensive chemotherapy.
Descriptive summary of plasma concentrations and PK parameters of revumenib and the primary metabolites.
Descriptive summary of revumenib pharmacodynamics in relation to safety, efficacy and correlative biomarkers, which may include immunophenotyping of circulating peripheral blood mononuclear cells (PBMC) and/or bone marrow, gene expression, mutational analysis, and minimal residual disease (MRD).
Frequency and severity of AE according to CTCAE version 5.0.
Time to hematopoietic recovery (absolute neutrophil counts 0.5 and 1.0 x 109/L; platelets 50 and 100 x 109/L) after each treatment cycle (but at least for each of the first 6 cycles), defined as the time from the start of the cycle until recovery.
Number of patients requiring transfusions (platelet and RBC) and number of units transfused, rate and duration of transfusion independence, length of hospital stay, where transfusion independence is defined as a period of at least 56 days with no transfusion between the first dose of study drug and the last dose of study drug + 30 days.
Rates of CRMRD-, CR/CRhMRD-, and CR/CRiMRD- assessed by quantitative PCR of peripheral blood in adult patients with newly diagnosed NPM1-mutated AML ineligible for intensive chemotherapy, defined as the proportion of NPM1-mutated AML patients with CRMRD-, CR/CRhMRD- and CR/CRiMRD- by PCR in peripheral blood, respectively, at any time-point during protocol therapy.

Temporary moments of secondary assessment

Not provided

Inclusion criteria

Patient with newly diagnosed NPM1-mutated AML, consistent with NPM1c, according to the 2022 International Consensus Classification (i.e. 10% blasts). OR Patient with newly diagnosed KMT2A-rearranged AML according to the 2022 International Consensus Classification (i.e. 10% blasts). KMT2A partial tandem duplications or deletions are NOT eligible. Of note: in case both NPM1 and IDH1 are mutated and both EVOLVE-1 (HO173) and EVOLVE-2 (HO177) are open for inclusion at your site, then patients can only be included in the EVOLVE-1 trial (HO173) Men must use a latex condom during any sexual contact with women of childbearing potential (WOCBP), even if they have undergone a successful vasectomy and must agree to avoid to father a child (while on therapy and for 6 months after the final study drug administration). In addition, their female partners of childbearing potential must use a highly effective method of birth control. Male patient must not donate sperm starting at screening and throughout the study period and for 6 months after the final study drug administration. Able to understand and willing to sign an informed consent form (ICF). Institutional Review Board/Independent Ethics Committee-approved written informed consent as per national regulations must be obtained from the patient prior to any study-related procedures (including consent for withdrawal of prohibited medication, if applicable). Central confirmation of NPM1 mutation or KMT2A rearrangement in one of the dedicated central genetic laboratories. Age 18 years, no upper age limit. Patient is ineligible for intensive induction chemotherapy by meeting at least 1 of the following criteria: 75 years of age: ineligible for intensive chemotherapy per physicians discretion (with an ECOG performance status 0-2) 18-74 years: patient is not eligible for standard chemotherapy because any of the following co-morbidities: ECOG performance status 2 or 3 Cardiac history of chronic heart failure requiring treatment; or with an ejection fraction 50%; or chronic stable angina. DLCO 65% or FEV1 65%. Creatinine clearance 30 mL/min to <45 ml/min calculated by the Cockcroft Gault formula. Moderate hepatic impairment with total bilirubin > 1.5 to < 3.0 x upper limit of normal (ULN). Any other comorbidity that the local physician assesses to be incompatible with intensive chemotherapy. Patient must have a

projected life expectancy of at least 12 weeks (as assessed by the treating physician). Patient must have a white cell blood (WBC) count of < 25 x 109/L. Hydroxyurea can be used prior to study enrollment to reduce the WBC count to meet this criterion. Adequate renal function as evidenced by serum creatinine 2.0 × upper limit of norm (ULN) or creatinine clearance >30 mL/min based on the Cockcroft-Gault glomerular filtration rate (GFR). Adequate hepatic function as evidenced by: Serum total bilirubin 3.0 × ULN unless considered due to Gilberts disease, or leukemic involvement; Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) 3.0 × ULN, unless considered due to leukemic involvement. Female patient must: be of nonchildbearing potential: or, if of childbearing potential (not surgically sterile and not postmenopausal) agree to avoid pregnancy during the study and for 6 months after the final study drug administration; and have a negative urine or serum pregnancy test at screening; and, if heterosexually active, agree to consistently apply one highly effective method of birth control for the duration of the study and for 6 months after the final study drug administration; agree not to breastfeed starting at screening and throughout the study period, and for 1 week after the final study drug administration; agree not to donate ova starting at screening and throughout the study period, and for 6 months after the final study drug administration.

Exclusion criteria

Subject has previously been treated for AML; a treatment period with hydroxyurea to control WBC counts is allowed; prior treatment with a hypomethylating agent for MDS-EB is not allowed; prior treatment with erythropoiesis-stimulating agents or luspatercept for MDS is allowed. The patient is a pregnant or lactating woman, or plans to become pregnant during the study. Patient who has once been screened and randomized into this HO177 trial but was considered ineligible cannot re-enter this trial at a later date. Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2); PML-RARA; or one of the other pathognomonic variant chromosomal translocations / fusion genes. AML with BCR-ABL1; or myeloid blast crisis of CML. Significant active cardiac disease within 3 months prior to the start of study treatment, including: New York Heart Association (NYHA) class III or IV congestive heart failure Myocardial infarction Unstable angina Severe cardiac arrhythmias Congenital long QT syndrome of family member with this condition QTcF >450 msec on screening electrogram for males and >470msec on screening electrogram for females (mean of triplicate recordings; calculated using Fridericias correction). Severe obstructive or restrictive ventilation disorder. History of stroke or intracranial hemorrhage within 6 months prior to randomization. Clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid (CSF) during screening is only required if there is a clinical suspicion of CNS involvement by leukemia during screening. Active infection, including hepatitis B or hepatitis C or Human Immunodeficiency Virus (HIV) infection, that is uncontrolled prior to first dose of study treatment and may interfere with the study objectives or which could expose the patient to undue risk through the participation in the clinical trial; an infection controlled with an approved antibiotic/ antiviral/ antifungal treatment that is not a strong or moderate CYP3A inducer is allowed. Immediate life-threatening, severe complications of leukemia such as uncontrolled bleeding and/or disseminated intravascular coagulation. Conditions that limit the ingestion or gastrointestinal absorption of orally administered drugs. Patient weighing <40 kg at registration. Patient with a currently active second malignancy. Patients are not considered to have a currently active malignancy, if they have completed therapy and are considered by their physician to be at < 30% risk of relapse within one year. However, patients with the following history/concurrent conditions are allowed: Basal or squamous cell carcinoma of the skin; Carcinoma in situ of the cervix; Carcinoma in situ of the breast; Incidental histologic finding of prostate cancer. Receipt of live, attenuated vaccine within 30 days prior to the study inclusion (NOTE: patient, if enrolled, should not receive live vaccine during the study and until 6 months after the therapy). Severe neurological or psychiatric disorder interfering with ability to give an informed consent. Contraindication to azacitidine or venetoclax Participation in other prospective studies with anti-leukemic and/or investigational agents. Patient taking Dabigatran unless they can be transferred to other medications within 5 half-lives prior to dosing. Patients taking other P-gP transporter-sensitive medications should be properly monitored during the study if they cannot be transferred to other medications Patients taking known strong cytochrome P450 (CYP) 3A4 inducers, unless they can be transferred to other medications within 5 half-lives prior to dosing.

Calendar

(Last Update: 26/05/2026)

Authorization	Start of Trial	First patient inclusion	Halted	Restarted
06/08/2025	12/12/2025	24/03/2026	Not aported	Not aported

End of recruitment	Premature end (Spain)	Premature End (Global)	Trial end (Spain)	Trial end (Global)
Not aported	Not aported	Not aported	Not aported	Not aported

Sponsor

Hemato-Oncologie voor Volwassenen Nederland (Hovon) Stichting Netherlands

Dr. Molewaterplein 40

Contact Person

HOVON

0031107041560

hovon@erasmusmc.nl

Monetary support: N/A

Sponsor type: No commercial

Ceim

CEIm Fundacio de Gestio Sanitaria Hospital de la Santa Creu i Sant Pau

C/ Sant Quintí, 77-79. Planta 1a. Despacho 95 08041 Barcelona

ceimsantpau@santpau.cat

935537813

Sites

Active (28/01/2026)

Fundacio Assistencial De Mutua De Terrassa Fpc

Terrassa

BARCELONA

Haematology

Active (23/12/2025)

Hospital Clinic De Barcelona

Barcelona

BARCELONA

Haematology

Active (16/12/2025)

Hospital Clinico Universitario De Valencia

Valencia

VALENCIA

Haematology

Active (05/02/2026)

Hospital De La Santa Creu I Sant Pau

Barcelona

BARCELONA

Haematology

Active (06/03/2026)

Hospital Del Mar

Barcelona

BARCELONA

Haematology

Active (16/02/2026)

Hospital General Universitario Gregorio Maranon

Madrid

MADRID

Haematology

Active (12/12/2025)

Hospital Universitari Arnau De Vilanova De La Gerencia Territorial De Lleida

Lleida

LÉRIDA

Haematology

not initialized (--/--/----)

Hospital Universitari Joan XXIII De Tarragona

Tarragona

TARRAGONA

Haematology

Active (20/03/2026)

Institut Catala D´oncologia

Girona

GERONA

Haematology

Active (24/03/2026)

Institut Catala D´oncologia

L'hospitalet De Llobregat

BARCELONA

Haematology

Active (24/02/2026)

Institut Catala D´oncologia

Badalona

BARCELONA

Haematology

Active (19/02/2026)

University Hospital Son Espases

Palma

BALEARES

Haematology

Medication

Venclyxto 10 mg film-coated tablets
FILM-COATED TABLET
ORAL

ATC code: L01XX52 - VENETOCLAX
Active Principles: N/A

Experimental

Venclyxto 10 mg film-coated tablets
FILM-COATED TABLET
ORAL

ATC code: L01XX52 - VENETOCLAX
Active Principles: N/A

Experimental

Revumenib
TABLET
ORAL USE

-
Active Principles: N/A

Experimental

Revumenib
TABLET
ORAL

-
Active Principles: N/A

Experimental

Venclyxto 100 mg film-coated tablets
FILM-COATED TABLET
ORAL

ATC code: L01XX52 - VENETOCLAX
Active Principles: N/A

Experimental

Revumenib
TABLET
ORAL

-
Active Principles: N/A

Experimental

Revumenib
TABLET
ORAL

-
Active Principles: N/A

Experimental

Azacitidine Seacross 25 mg/mL powder for suspension for injection
SUSPENSION FOR INJECTION
SUBCUTANEOUS

ATC code: L01BC07 - AZACITIDINA
Active Principles: N/A

Experimental

Venclyxto 100 mg film-coated tablets
FILM-COATED TABLET
ORAL

ATC code: L01XX52 - VENETOCLAX
Active Principles: N/A

Experimental

Venclyxto 50 mg film-coated tablets
FILM-COATED TABLET
ORAL

ATC code: L01XX52 - VENETOCLAX
Active Principles: N/A

Experimental

Venclyxto 50 mg film-coated tablets
FILM-COATED TABLET
ORAL

ATC code: L01XX52 - VENETOCLAX
Active Principles: N/A

Experimental

Azacitidine Seacross 25 mg/mL powder for suspension for injection
SUSPENSION FOR INJECTION
SUBCUTANEOUS

ATC code: L01BC07 - AZACITIDINA
Active Principles: N/A

Experimental

Revumenib
TABLET
ORAL USE

-
Active Principles: N/A

Experimental

Revumenib
TABLET
ORAL

-
Active Principles: N/A

Experimental

No results