# Ziftomenib in combination with chemotherapy for children with relapsed/refractory acute leukemia

| Estado | Tipo de Participantes | Rangos de Edad |
|---|---|---|
| Reclutando | Sujetos incapaces de otorgar consentimiento | Menores de 18 , Adultos (18-64 años) , Adolescentes (12-17 años) , Niños (2-11 años) , Lactantes y preescolar (28 días - 23 meses) , Recién nacidos (0-27 días) |
| **Género** | **Fases** | **Participantes esperados** |
| Ambos | Fase I | 10 |
| **Resultados** | **Bajo nivel intervención** | **Enfermedad rara** |
| Sin resultados | No | Si |
| **Cobertura geográfica** | **Ámbitos del ensayo** | **Terapia avanzada** |
| Sin determinar | tratamiento, seguridad, eficacia, farmacocinética, farmacodinamica, dosis | NO |

## Información

### Identificador
2023-505262-28-00 (CTIS)

### Cod. Protocolo
No aportado

### Área terapéutica
Enfermedades [C] - Hematología [C15]|

### Enfermedad investigada
Acute Myeloid Leukemia
Mixed Phenotype Acute Leukemia
Acute Lymphocytic Leukemia

### Título Científico
A Phase 1 Trial of the Menin Inhibitor Ziftomenib in Combination with Chemotherapy for Children with

Relapsed/Refractory KMT2A-rearranged, NUP98-rearranged, or NPM1-mutant Acute Leukemia

## Justificación

No aportado

## Objetivo Principal

To determine the recommended phase 2 dose (RP2D) of ziftomenib in combination with chemotherapy (FLA) in children with relapsed or refractory KMT2A-r, NUP98-r, or NPM1-m acute leukemia based on safety and pharmacokinetics (PK).

## Variables de Evaluación Primaria

The primary endpoint is determination of the RP2D based on: Dose-limiting toxicities (DLTs) assessed during the first cycle of treatment.; Pharmacokinetic parameters of ziftomenib: AUC.

## Momentos temporales de evaluación primaria

No aportado

## Objetivo Secundario

To describe the safety and tolerability of ziftomenib administered in combination with chemotherapy (FLA) (and/or a 2nd cycle when needed)
To evaluate the safety and tolerability profile during the prolonged exposure (max. 12 cycles of 28 days) to ziftomenib
To evaluate the safety and tolerability profile in patients receiving ziftomenib post-HSCT (max. 12 cycles of ziftomenib)
To determine the pharmacokinetics (PK) of ziftomenib, also in relationship to age
To describe the hematopoietic stem cell transplant (HSCT) rate
To describe the anti-leukemic activity in pediatric patients with relapsed or refractory KMT2A-r, NUP98-r, or NPM1-m acute leukemia overall and per disease subset (AML and ALL)

## Variables de Evaluación Secundaria

Adverse events (AEs), as characterized by type, frequency, severity (as graded using CTCAE version 5.0), timing, seriousness, and relation to study therapy.
AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v5.0), timing, seriousness, and relation to study therapy during prolonged exposure
AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v5.0), timing, seriousness, and relation to study therapy post HSCT
PK of ziftomenib in combination with FLA chemotherapy: PK parameters of ziftomenib including Cmax, Cmin, Tmax,

AUC0-t, AUC0-, CL/F, Vz/F, and t½
The rate of those proceeding to subsequent hematopoietic stem cell transplantation as consolidation therapy is calculated as the number of patients who receive a hematopoietic stem cell infusion divided by the total number of patients enrolled and started treatment.
The following parameters will be studied: Morphological ORR, defined as CR plus CRp and CRi (defined in Section 11.2.1); Flow-based overall response rate (ORR, defined in Section 11.2.1); Flow-based Measurable Residual Disease (MRD) negativity rate; Duration of response (DOR); Event free survival (EFS): 1 year after EOT of the last patient with ziftomenib; Overall survival (OS): 1 year after EOT of the last patient with ziftomenib; Cumulative incidence of relapse (CIR): 1 year after EOT

## Momentos temporales de evaluación secundaria

No aportado

## Criterios de Inclusión

Age: 0-21 years (and at least 5 kg BW), with a minimum of 80% of patients under 18 years of age Female patients with infants must agree not to breastfeed their infants while on this study. Contraception: a. Patients of reproductive potential, starting from menarche and onwards, may not participate unless they have agreed to use a highly effective contraceptive method per Clinical Trial Facilitation Group (CTFG) guidelines for the duration of study therapy and for 6 months after the completion of all study therapy. For further guidance please review the CTFG website. b. Male patients must use a condom during intercourse and agree not to father a child or donate sperm during therapy and for the duration of study therapy and for 6 months after the completion of all study therapy. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. d) Interleukins, interferons and cytokines (other than hematopoietic growth factors): 21 days after the completion of interleukins, interferon or cytokines (other than hematopoietic growth factors). Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. e) Hematopoietic growth factors: 14 days after the last dose of a long-acting growth factor (e.g., peg-filgrastim) or 7 days for short-acting growth factor. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. f) Radiation therapy (RT): 14 days have elapsed for local palliative RT (small port); 84 days must have elapsed if prior craniospinal RT or if 50% radiation of pelvis; 42 days must have elapsed if other substantial BM radiation. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. Stem Cell Infusions: a. Patients who have relapsed after allogeneic (non-autologous) bone marrow or stem cell transplant (with or without TBI) or boost infusion (any stem cell product; not including DLI) must be at least 84 days post HSCT and without evidence of GVHD of any severity except: the use of topical steroids for cutaneous GVHD is allowed and stable steroid doses less than or equal to 10 mg of prednisone daily is permitted. Prednisone dose must be adjusted for BSA in young children. Physiologic doses of hydrocortisone for patients with adrenal insufficiency is allowed. b. Patients who after relapse and continue to receive cyclosporine, tacrolimus or other agents to treat or prevent either graft-versus-host disease post bone marrow transplant or organ rejection post-transplant are not eligible for this trial. In the relapse setting, patients must be off medications to treat or prevent either graft-versus-host disease post bone marrow transplant or organ rejection post-transplant for at least 14 days prior to enrollment. A stable steroid dose as mentioned above is allowed. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not

considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. h) Cellular therapy: 30 days after the completion of DLI (donor lymphocyte infusion) or any type of cellular Therapy (e.g., modified T cells, NK cells, dendritic cells, etc.). Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. i) Prior exposure to a different menin inhibitor: Patients who received previous treatment with a different menin inhibitor are allowed to enrol in the study with the exception of those who experienced a severe adverse event attributable to the strong anti-proliferative/pro-differentiation effects of other menin inhibitors (such as severe differentiation syndrome). Patients who experienced a severe adverse event, which can directly be attributed to specific effects (e.g., long QT syndrome) observed with other menin inhibitors can participate in the study if they fulfill the inclusion criteria. Diagnosis: KMT2A-r, NPM1-m, or NUP98-r acute leukemia in first or greater relapse or refractory to standard (re-) induction treatment (including HSCT). Eligible patients also must fulfill one of the following conditions: First or subsequent relapse: a) Bone marrow relapse is defined as: i) a single bone marrow sample or bone biopsy showing 5% leukemic blasts by local morphology b) Patients with combined extramedullary and bone marrow relapse (defined as above) are eligible. c) d) Patients with asymptomatic CNS3 disease are eligible if they do not have isolated CNS3 extramedullary relapse, see for definition section 7.8. Eligible patients also must fulfill one of the following conditions: Refractory disease/induction failure: a) AML: The bone marrow contains 5% leukemic blasts by local morphology at the end of 2 cycles of induction therapy. ALL/MPAL/AUL: The bone marrow contains 5% leukemic blasts by local morphology MFC at the end of induction and consolidation Enrollment APAL2020SC trial (US and Canada only): Patients in the US and Canada must have enrolled in the APAL2020SC trial prior to enrollment in the APAL2020K trial. Performance Status: Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2 ( 50% Lansky or Karnofsky score). Use ECOG for adult patients (18 to 21 years), Karnofsky for patients 16 to 18 years of age, and Lansky for patients < 16 years of age. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. Adequate Organ Function: a) Renal Function Defined as: creatinine clearance (CrCl) 60 mL/min (as measured by a nuclear glomerular filtration rate [GFR] scan or calculated by the Schwartz formula (APPENDIX III The Schwartz formula) and normalized to a body surface area of 1.73 m2)[71]. b) Liver Function Defined as: Direct bilirubin < 3 x ULN and SGPT (ALT) 5 x ULN. If liver abnormality is due to radiographically identifiable leukemia infiltrate, the patient will remain eligible. c) Cardiac function defined as: Pre-treatment left ventricular function on echocardiography: FS 25% or EF 40%, and no signs of congestive heart failure within 4 weeks before start of screening. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. a) Cytotoxic chemotherapy: Must not have received within 14 days or within 5 drug half-lives (whichever is longer), of entry onto this study, except for hydroxyurea or corticosteroids. Use of steroids and hydroxyurea for other purposes such as differentiation syndrome, or to premedication to prevent allergic reaction or during anesthesia is allowed. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. b) Intrathecal cytotoxic therapy: No washout or waiting period is required for patients having received any combination of intrathecal cytarabine, methotrexate, and/or hydrocortisone. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. c) Antibodies: 21 days must have elapsed from infusion of last dose of an antibody-drug conjugate. For unmodified antibodies or T cell engaging antibodies, 2 half-lives must have elapsed before enrollment. Any toxicity related to prior antibody therapy must be recovered back to baseline. Informed Consent: Written, signed and dated informed consent and pediatric assent (if applicable) according to local law and legislation should be collected before start of any study procedures Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed prior to enrollment.

## Criterios de Exclusión

Patients who in the opinion of the investigator may not be able to comply with the study requirements of the study.
Patients with known prior allergy to any of the medications used in protocol therapy.
Patients with documented active, uncontrolled infection at the time of study entry.
Active/uncontrolled known human immunodeficiency virus (HIV) infection, HBV and HCV. Note: HIV testing does not need to be conducted at screening unless it is required per local guidelines or institutional standard.
Post menarche female patients with positive pregnancy test, and a lactating female patient.
Patient has a pre-existing disorder predisposing the patient to a serious or life-threatening infection (e.g., cystic fibrosis, congenital or acquired immunodeficiency, bleeding disorder, or cytopenia not related to the leukemia or its treatment).
Patients must not be receiving other investigational medications (defined as medicinal products not yet approved for any indications, including alternative/herbal therapies) within 30 days of first dose of study drug or while on study.
Significant congenital cardiovascular disease including, but not limited to conditions such as long QT syndrome, fundamental uncorrected cardiac defect (e.g., coarctation of the aorta) that poses a significant risk to the patient (ventricular septal defect or atrial septal defect are considered non-significant).
Underlying medical condition that, in the Principal Investigators opinion, will make the administration of study treatment hazardous or obscure the interpretation of toxicity determination or adverse events (AEs).
For fluadarabine and cytarabine: Hypersensitivity to the active substance or to any of the excipients
Recent live vaccinations for at least 6 months.
Patients with Down syndrome.
Patients with isolated extramedullary disease (EMD) are not eligible. EMD relapse is defined as biopsy proven extramedullary disease without bone marrow disease after documented CR following initial therapy.
Patients with isolated CNS relapse are not eligible, as well as symptomatic CNS3 disease.
Patients with acute promyelocytic leukemia (APL) or juvenile myelomonocytic leukemia (JMML).
Patients with malabsorption syndrome or any other condition that precludes enteral administration of a menin inhibitor.
Concommittant Therapy: Gastric pH has great influence on absorption of ziftomenib; therefore, the use of proton pump inhibitors is prohibited, if necessary H2 Blockers may provide an alternative treatment option (for details see chapter 1.6 drug-drug interactions)
Patients who are currently receiving another investigational drug.
Patients with any known congenital bone marrow failure syndrome.

# Calendario

(Última actualización: 15/10/2025)

| Autorización | Inicio de Ensayo | Inclusión Primer Paciente | Interrumpido | Reiniciado |
|---|---|---|---|---|
| 02/12/2024 | 24/03/2025 | 13/10/2025 | 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

### Prinses Maxima Centrum voor Kinderoncologie B.V. Netherlands

**Heidelberglaan 25**

**Contact Person**

TDC Secretary

**+31889227272**

**TDCSecretary@prinsesmaximacentrum.nl**

**Monetary support: N/A**

**Tipo de promotor: No comercial**

# Ceim

### CEIm Hospital Clínico San Carlos

**C/ Doctor Martín Lagos, s/n - Ciudad Universitaria 28040 Madrid**

**ceic.hcsc@salud.madrid.org**

**917044160**

# Centros

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

### Hospital Infantil Universitario Nino Jesus

Madrid

MADRID

Pediatric Oncology and Hematology

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

### Hospital Universitari Vall D Hebron

Barcelona

BARCELONA

Pediatric Oncology and Hematology

# Medicamentos

### Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion

SOLUTION FOR INJECTION/INFUSION

INTRAVENOUS

Código ATC: L01BB05 - FLUDARABINA

Principios Activos: N/A

Experimental

### Cytarabine 20 mg/ml Solution for Injection/Infusion

SOLUTION FOR INJECTION/INFUSION

INTRAVENOUS

Código ATC: L01BC01 - CITARABINA

Principios Activos: N/A

Experimental

### Cytarabine 20 mg/ml Solution for Injection/Infusion

SOLUTION FOR INJECTION/INFUSION

INTRAVENOUS

Código ATC: L01BC01 - CITARABINA

Principios Activos: N/A

Experimental

### Ziftomenib

CAPSULE, HARD

ORAL

-

Principios Activos: N/A

Huérfano

Experimental

### Ziftomenib

CAPSULE, HARD

ORAL

-

Principios Activos: N/A

Huérfano

Experimental

### Solu-Cortef Powder for Solution for Injection or Infusion 100 mg

SOLUTION FOR INJECTION/INFUSION

INTRATHECAL USE

Código ATC: H02AB09 - HIDROCORTISONA

Principios Activos: N/A

Experimental

### Ziftomenib

CAPSULE, HARD

ORAL

-

Principios Activos: N/A

Huérfano

Experimental

# Sin resultados

# Ziftomenib in combination with chemotherapy for children with relapsed/refractory acute leukemia

| State | Type of participants | Age Ranges |
|---|---|---|
| Recruiting | Incapable subjects of giving consent | Less than 18 , Adults (18-64 years) , Teens (12-17 years) , Children (2-11 years) , Infants and preschool (28 days - 23 months) , Newborn infants (0-27 days) |
| **Gender** | **Phases** | **Expected Participants** |
| Both | Phase I | 10 |
| **Results** | **Low level of intervention** | **Rare disease** |
| No results | No | Yes |
| **Geographic coverage** | **Areas of the study** | **Advanced therapy** |
| Undetermined | treatment, safety, effectiveness, pharmacokinetics, pharmacodynamics, dose | NO |

## Information

### Identifier
2023-505262-28-00 (CTIS)

### Protocol Code
No aportado

### Therapeutic area
Diseases [C] - Hemic and Lymphatic Diseases [C15]|

### Investigated Disease
Acute Myeloid Leukemia
Mixed Phenotype Acute Leukemia
Acute Lymphocytic Leukemia

### Scientific Title
A Phase 1 Trial of the Menin Inhibitor Ziftomenib in Combination with Chemotherapy for Children with

Relapsed/Refractory KMT2A-rearranged, NUP98-rearranged, or NPM1-mutant Acute Leukemia

## Rationale

Not provided

## Main Objective

To determine the recommended phase 2 dose (RP2D) of ziftomenib in combination with chemotherapy (FLA) in children with relapsed or refractory KMT2A-r, NUP98-r, or NPM1-m acute leukemia based on safety and pharmacokinetics (PK).

## Primary Endpoints

The primary endpoint is determination of the RP2D based on: Dose-limiting toxicities (DLTs) assessed during the first cycle of treatment.; Pharmacokinetic parameters of ziftomenib: AUC.

## Temporary moments of secondary assessment

Not provided

## Secondary Objective

To describe the safety and tolerability of ziftomenib administered in combination with chemotherapy (FLA) (and/or a 2nd cycle when needed)
To evaluate the safety and tolerability profile during the prolonged exposure (max. 12 cycles of 28 days) to ziftomenib
To evaluate the safety and tolerability profile in patients receiving ziftomenib post-HSCT (max. 12 cycles of ziftomenib)
To determine the pharmacokinetics (PK) of ziftomenib, also in relationship to age
To describe the hematopoietic stem cell transplant (HSCT) rate
To describe the anti-leukemic activity in pediatric patients with relapsed or refractory KMT2A-r, NUP98-r, or NPM1-m acute leukemia overall and per disease subset (AML and ALL)

## Secondary Endpoints

Adverse events (AEs), as characterized by type, frequency, severity (as graded using CTCAE version 5.0), timing, seriousness, and relation to study therapy.
AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v5.0), timing, seriousness, and relation to study therapy during prolonged exposure
AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v5.0), timing, seriousness, and relation to study therapy post HSCT
PK of ziftomenib in combination with FLA chemotherapy: PK parameters of ziftomenib including Cmax, Cmin, Tmax,

AUC0-t, AUC0-, CL/F, Vz/F, and t½
The rate of those proceeding to subsequent hematopoietic stem cell transplantation as consolidation therapy is calculated as the number of patients who receive a hematopoietic stem cell infusion divided by the total number of patients enrolled and started treatment.
The following parameters will be studied: Morphological ORR, defined as CR plus CRp and CRi (defined in Section 11.2.1); Flow-based overall response rate (ORR, defined in Section 11.2.1); Flow-based Measurable Residual Disease (MRD) negativity rate; Duration of response (DOR); Event free survival (EFS): 1 year after EOT of the last patient with ziftomenib; Overall survival (OS): 1 year after EOT of the last patient with ziftomenib; Cumulative incidence of relapse (CIR): 1 year after EOT

## Temporary moments of secondary assessment

Not provided

## Inclusion criteria

Age: 0-21 years (and at least 5 kg BW), with a minimum of 80% of patients under 18 years of age Female patients with infants must agree not to breastfeed their infants while on this study. Contraception: a. Patients of reproductive potential, starting from menarche and onwards, may not participate unless they have agreed to use a highly effective contraceptive method per Clinical Trial Facilitation Group (CTFG) guidelines for the duration of study therapy and for 6 months after the completion of all study therapy. For further guidance please review the CTFG website. b. Male patients must use a condom during intercourse and agree not to father a child or donate sperm during therapy and for the duration of study therapy and for 6 months after the completion of all study therapy. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. d) Interleukins, interferons and cytokines (other than hematopoietic growth factors): 21 days after the completion of interleukins, interferon or cytokines (other than hematopoietic growth factors). Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. e) Hematopoietic growth factors: 14 days after the last dose of a long-acting growth factor (e.g., peg-filgrastim) or 7 days for short-acting growth factor. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. f) Radiation therapy (RT): 14 days have elapsed for local palliative RT (small port); 84 days must have elapsed if prior craniospinal RT or if 50% radiation of pelvis; 42 days must have elapsed if other substantial BM radiation. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. Stem Cell Infusions: a. Patients who have relapsed after allogeneic (non-autologous) bone marrow or stem cell transplant (with or without TBI) or boost infusion (any stem cell product; not including DLI) must be at least 84 days post HSCT and without evidence of GVHD of any severity except: the use of topical steroids for cutaneous GVHD is allowed and stable steroid doses less than or equal to 10 mg of prednisone daily is permitted. Prednisone dose must be adjusted for BSA in young children. Physiologic doses of hydrocortisone for patients with adrenal insufficiency is allowed. b. Patients who after relapse and continue to receive cyclosporine, tacrolimus or other agents to treat or prevent either graft-versus-host disease post bone marrow transplant or organ rejection post-transplant are not eligible for this trial. In the relapse setting, patients must be off medications to treat or prevent either graft-versus-host disease post bone marrow transplant or organ rejection post-transplant for at least 14 days prior to enrollment. A stable steroid dose as mentioned above is allowed. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not

considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. h) Cellular therapy: 30 days after the completion of DLI (donor lymphocyte infusion) or any type of cellular Therapy (e.g., modified T cells, NK cells, dendritic cells, etc.). Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. i) Prior exposure to a different menin inhibitor: Patients who received previous treatment with a different menin inhibitor are allowed to enrol in the study with the exception of those who experienced a severe adverse event attributable to the strong anti-proliferative/pro-differentiation effects of other menin inhibitors (such as severe differentiation syndrome). Patients who experienced a severe adverse event, which can directly be attributed to specific effects (e.g., long QT syndrome) observed with other menin inhibitors can participate in the study if they fulfill the inclusion criteria. Diagnosis: KMT2A-r, NPM1-m, or NUP98-r acute leukemia in first or greater relapse or refractory to standard (re-) induction treatment (including HSCT). Eligible patients also must fulfill one of the following conditions: First or subsequent relapse: a) Bone marrow relapse is defined as: i) a single bone marrow sample or bone biopsy showing 5% leukemic blasts by local morphology b) Patients with combined extramedullary and bone marrow relapse (defined as above) are eligible. c) d) Patients with asymptomatic CNS3 disease are eligible if they do not have isolated CNS3 extramedullary relapse, see for definition section 7.8. Eligible patients also must fulfill one of the following conditions: Refractory disease/induction failure: a) AML: The bone marrow contains 5% leukemic blasts by local morphology at the end of 2 cycles of induction therapy. ALL/MPAL/AUL: The bone marrow contains 5% leukemic blasts by local morphology MFC at the end of induction and consolidation Enrollment APAL2020SC trial (US and Canada only): Patients in the US and Canada must have enrolled in the APAL2020SC trial prior to enrollment in the APAL2020K trial. Performance Status: Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2 ( 50% Lansky or Karnofsky score). Use ECOG for adult patients (18 to 21 years), Karnofsky for patients 16 to 18 years of age, and Lansky for patients < 16 years of age. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. Adequate Organ Function: a) Renal Function Defined as: creatinine clearance (CrCl) 60 mL/min (as measured by a nuclear glomerular filtration rate [GFR] scan or calculated by the Schwartz formula (APPENDIX III The Schwartz formula) and normalized to a body surface area of 1.73 m2)[71]. b) Liver Function Defined as: Direct bilirubin < 3 x ULN and SGPT (ALT) 5 x ULN. If liver abnormality is due to radiographically identifiable leukemia infiltrate, the patient will remain eligible. c) Cardiac function defined as: Pre-treatment left ventricular function on echocardiography: FS 25% or EF 40%, and no signs of congestive heart failure within 4 weeks before start of screening. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. a) Cytotoxic chemotherapy: Must not have received within 14 days or within 5 drug half-lives (whichever is longer), of entry onto this study, except for hydroxyurea or corticosteroids. Use of steroids and hydroxyurea for other purposes such as differentiation syndrome, or to premedication to prevent allergic reaction or during anesthesia is allowed. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. b) Intrathecal cytotoxic therapy: No washout or waiting period is required for patients having received any combination of intrathecal cytarabine, methotrexate, and/or hydrocortisone. Prior Therapy: Patients must have recovered from the acute toxic effects of all prior anti-cancer Therapy (excluding Grade 2 toxicities that are not considered a safety risk or medically significant toxicity deemed irreversible by the Investigator) and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. c) Antibodies: 21 days must have elapsed from infusion of last dose of an antibody-drug conjugate. For unmodified antibodies or T cell engaging antibodies, 2 half-lives must have elapsed before enrollment. Any toxicity related to prior antibody therapy must be recovered back to baseline. Informed Consent: Written, signed and dated informed consent and pediatric assent (if applicable) according to local law and legislation should be collected before start of any study procedures Female patients of childbearing potential must have a negative urine or serum pregnancy test confirmed prior to enrollment.

## Exclusion criteria

Patients who in the opinion of the investigator may not be able to comply with the study requirements of the study.
Patients with known prior allergy to any of the medications used in protocol therapy.
Patients with documented active, uncontrolled infection at the time of study entry.
Active/uncontrolled known human immunodeficiency virus (HIV) infection, HBV and HCV. Note: HIV testing does not need to be conducted at screening unless it is required per local guidelines or institutional standard.
Post menarche female patients with positive pregnancy test, and a lactating female patient.
Patient has a pre-existing disorder predisposing the patient to a serious or life-threatening infection (e.g., cystic fibrosis, congenital or acquired immunodeficiency, bleeding disorder, or cytopenia not related to the leukemia or its treatment).
Patients must not be receiving other investigational medications (defined as medicinal products not yet approved for any indications, including alternative/herbal therapies) within 30 days of first dose of study drug or while on study.
Significant congenital cardiovascular disease including, but not limited to conditions such as long QT syndrome, fundamental uncorrected cardiac defect (e.g., coarctation of the aorta) that poses a significant risk to the patient (ventricular septal defect or atrial septal defect are considered non-significant).
Underlying medical condition that, in the Principal Investigators opinion, will make the administration of study treatment hazardous or obscure the interpretation of toxicity determination or adverse events (AEs).
For fluadarabine and cytarabine: Hypersensitivity to the active substance or to any of the excipients
Recent live vaccinations for at least 6 months.
Patients with Down syndrome.
Patients with isolated extramedullary disease (EMD) are not eligible. EMD relapse is defined as biopsy proven extramedullary disease without bone marrow disease after documented CR following initial therapy.
Patients with isolated CNS relapse are not eligible, as well as symptomatic CNS3 disease.
Patients with acute promyelocytic leukemia (APL) or juvenile myelomonocytic leukemia (JMML).
Patients with malabsorption syndrome or any other condition that precludes enteral administration of a menin inhibitor.
Concommittant Therapy: Gastric pH has great influence on absorption of ziftomenib; therefore, the use of proton pump inhibitors is prohibited, if necessary H2 Blockers may provide an alternative treatment option (for details see chapter 1.6 drug-drug interactions)
Patients who are currently receiving another investigational drug.
Patients with any known congenital bone marrow failure syndrome.

# Calendar

(Last Update: 15/10/2025)

| Authorization | Start of Trial | First patient inclusion | Halted | Restarted |
|---|---|---|---|---|
| 02/12/2024 | 24/03/2025 | 13/10/2025 | 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

### Prinses Maxima Centrum voor Kinderoncologie B.V. Netherlands

**Heidelberglaan 25**

**Contact Person**

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**+31889227272**

**TDCSecretary@prinsesmaximacentrum.nl**

**Monetary support: N/A**

**Sponsor type: No commercial**

# Ceim

### CEIm Hospital Clínico San Carlos

**C/ Doctor Martín Lagos, s/n - Ciudad Universitaria 28040 Madrid**

**ceic.hcsc@salud.madrid.org**

**917044160**

# Sites

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

### Hospital Infantil Universitario Nino Jesus

Madrid

MADRID

Pediatric Oncology and Hematology

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

### Hospital Universitari Vall D Hebron

Barcelona

BARCELONA

Pediatric Oncology and Hematology

# Medication

### Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion

SOLUTION FOR INJECTION/INFUSION

INTRAVENOUS

ATC code: L01BB05 - FLUDARABINA

Active Principles: N/A

Experimental

### Cytarabine 20 mg/ml Solution for Injection/Infusion

SOLUTION FOR INJECTION/INFUSION

INTRAVENOUS

ATC code: L01BC01 - CITARABINA

Active Principles: N/A

Experimental

### Cytarabine 20 mg/ml Solution for Injection/Infusion

SOLUTION FOR INJECTION/INFUSION

INTRAVENOUS

ATC code: L01BC01 - CITARABINA

Active Principles: N/A

Experimental

### Ziftomenib

CAPSULE, HARD

ORAL

-

Active Principles: N/A

Orphan

Experimental

### Ziftomenib

CAPSULE, HARD

ORAL

-

Active Principles: N/A

Orphan

Experimental

### Solu-Cortef Powder for Solution for Injection or Infusion 100 mg

SOLUTION FOR INJECTION/INFUSION

INTRATHECAL USE

ATC code: H02AB09 - HIDROCORTISONA

Active Principles: N/A

Experimental

### Ziftomenib

CAPSULE, HARD

ORAL

-

Active Principles: N/A

Orphan

Experimental

# No results