Bosutinib in pediatric CML patients

Estado	Tipo de Participantes	Rangos de Edad
Fin Reclutamiento	Sujetos incapaces de otorgar consentimiento	Menores de 18 , 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 , Fase II	60
Resultados	**Bajo nivel intervención**	**Enfermedad rara**
Sin resultados	No	Si
Cobertura geográfica	**Ámbitos del ensayo**	**Terapia avanzada**
Multicéntrico internacional	tratamiento, seguridad, eficacia, farmacocinética	NO

Información

Identificador
2023-504311-32-00 (CTIS)

Cod. Protocolo
ITCC-054/AAML1921

Transicionado 2015-002916-34

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

Enfermedad investigada
Chronic Myeloid Leukemia

Título Científico
A Phase I/II study of Bosutinib in pediatric patients with newly diagnosed chronic phase or resistant/intolerant Ph+ Chronic Myeloid Leukemia, study ITCC-054/COG AAML1921

Justificación

No aportado

Objetivo Principal

Phase 1: - To determine the Recommended Phase 2 Dose (RP2D) of bosutinib for R/I (RP2DR/I) and ND chronic phase (RP2DND) pediatric patients with CML, based on the pharmacokinetic, safety and tolerability profile of bosutinib observed at various dose levels in pediatric patients with CML who are resistant or intolerant to prior TKI therapy. Phase 2: - To assess the PK of bosutinib at the RP2DND and RP2DR/I in pediatric patients with ND or R/I Ph + CML. - To assess the population PK of bosutinib. - To assess the pooled safety and tolerability profile (based on AEs) of bosutinib in pediatric patients with ND and R/I Ph+ CML.

Variables de Evaluación Primaria

Phase 1: Incidence and severity of Dose-Limiting Toxicities (DLTs) assessed during the first 28 days of treatment.
Phase 1: PK parameters of bosutinib: Maximum observed plasma concentration (Cmax), time to Cmax (Tmax), area under the plasma concentration versus time curve from time zero to the dosing interval (AUC), pre-dose concentration (Ctrough) and apparent clearance (CL/F).
Phase 2: AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v4.03), timing, seriousness, and relation to study therapy (pooled across ND and R/I CML patients and by line of therapy).
Phase 2: PK parameters of bosutinib: Maximum observed plasma concentration (Cmax), time to Cmax (Tmax), area under the plasma concentration versus time curve from time zero the dosing interval (AUC), predose concentration (Ctrough) and apparent clearance CL/F.
Phase 2: Population PK parameters of bosutinib including clearance and volume of distribution based on combined PK data from Phase 1 and Phase 2.

Momentos temporales de evaluación primaria

No aportado

Objetivo Secundario

Phase 1: To evaluate the overall safety profile during the first cycle of therapy (28 days);
Phase 1: To evaluate the safety and tolerability profile during the prolonged exposure to bosutinib;
Phase 1: To preliminary evaluate the anti-leukemic activity in pediatric patients with Philadelphia chromosome positive CML following resistance or intolerance to one or more TKIs.
Phase 2: To describe the clinical efficacy of bosutinib in pediatric patients with newly diagnosed Ph+ CML in chronic phase;
Phase 2: To describe the clinical efficacy of bosutinib in pediatric patients with Ph + CML in any phase of disease following resistance or intolerance to one or more TKIs.
Phase 2: To assess other safety parameters of bosutinib
Phase 2: To assess the relationship between the PK of bosutinib and key safety and efficacy metrics.

Variables de Evaluación Secundaria

Phase 1: AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v4.03), timing, seriousness, and relation to study therapy;
Phase 1: Laboratory abnormalities as characterized by type, frequency, severity and timing;
Phase 1: ECG and performance status abnormalities
Phase 1: Overall cumulative disease response: complete hematologic response (CHR), major cytogenetic response (MCyR, defined as complete cytogenetic response [CCyR] plus partial cytogenetic response [PCyR]), CCyR, major molecular response (MMR) and deep molecular response.
Phase 2: Overall cumulative disease response by the line of therapy: complete hematologic response (CHR), major cytogenetic response (MCyR, defined as complete cytogenetic response [CCyR] plus partial cytogenetic response [PCyR]), CCyR, major molecular response (MMR) and deep molecular response.
Phase 2: Time to and duration of the respective responses by line of therapy.
Phase 2: Event-free survival (EFS; including time to transformation to AP and BP CML) by line of therapy.
Phase 2: Overall survival (OS) in pediatric patients with Ph+ CML by line of therapy.
Phase 2: Laboratory abnormalities as characterized by type, frequency, severity and timing (pooled across ND and R/I CML and by line of therapy).
Phase 2: ECG and performance status abnormalities.
Phase 2: Relationships between PK parameters of bosutinib and key safety and efficacy metrics.

Momentos temporales de evaluación secundaria

No aportado

Criterios de Inclusión

Phase 1 and Phase 2 (R/I patients): Cytogenetic and molecular diagnosis of Philadelphia chromosome-positive CML at either time of initial CML diagnosis or at time of study screening: 1. Cytogenetics must be performed by chromosome banding analysis (CBA) of bone marrow cell metaphases, and requires at least 20 metaphases. 2. Only if dividing marrow cells cannot be obtained, or if there is an insufficient number of metaphases, CBA can be substituted by interphase fluorescence in situ hybridization (I- FISH) of bone marrow or peripheral blood cells, using dual color dual fusion probes, that allow the detection of BCR-ABL+ nuclei; at least 200 nuclei should be counted. 3. Qualitative RT-PCR should be performed on RNA extracted from freshly collected bone marrow or peripheral blood cells. It identifies the transcript type, either e14a2 or 13a2 (also known as b3a2 and b2a2), or much more rarely e19a2, or e1a2, indicating the BCR- ABL protein weight (P210, rarely P230 or P190). Phase 1 and Phase 2 (R/I patients): Serum/urine pregnancy test (for all girls age of menarche) negative at screening. Phase 1 and Phase 2 (R/I patients): Male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 30 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active. Phase 1 and Phase 2 (R/I patients): Written informed consent of parent(s)/legal guardian(s) and/or patients (when applicable depending on age and local law and regulations). Phase 1 and Phase 2 (R/I patients): Patients (including legally acceptable representative for minors where applicable) who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Phase 2 (Newly Diagnosed CML patients): Cytogenetic and molecular diagnosis of Philadelphia chromosome-positive CML at either time of initial CML diagnosis or at time of study screening: 1. Cytogenetics must be performed by chromosome banding analysis (CBA) of bone marrow cell metaphases, and requires at least 20 metaphases. 2. Only if dividing marrow cells cannot be obtained, or if there is an insufficient number of metaphases, CBA can be substituted by interphase fluorescence in situ hybridization (I- FISH) of bone marrow or peripheral blood cells, using dual color dual fusion probes, that allow the detection of BCR-ABL+ nuclei; at least 200 nuclei should be counted. 3. Qualitative RT-PCR should be performed on RNA extracted from freshly collected bone marrow or peripheral blood cells. It identifies the transcript type, either e14a2 or e13a2 (also known as b3a2 and b2a2), or much more rarely

e19a2, or e1a2, indicating the BCR- ABL protein weight (P210, rarely P230 or P190). Phase 2 (Newly Diagnosed CML patients): Newly diagnosed CP Ph+ CML of 6 months (from initial diagnosis) without any previous TKI treatment (with the exception of hydroxyurea and/or anagrelide) for CML. Phase 2 (Newly Diagnosed CML patients): Age 1 and <18 years at day of attaining the informed consent. Phase 2 (Newly Diagnosed CML patients): Lansky performance status 50% for patients 16 years of age, or Karnofsky scale 50% for patients >16 years of age. Phase 2 (Newly Diagnosed CML patients): Adequate Renal Function: Subjects must have a calculated creatinine clearance (CrCl) 60 mL/min/1.73 m2, using the Schwartz formula to estimate GFR. Phase 2 (Newly Diagnosed CML patients): Adequate liver function, including: 1. AST/ALT 2.5 x upper limit normal (ULN) or 5 x ULN if attributable to disease involvement of the liver; 2. Total bilirubin 1.5 x ULN unless the patient has documented Gilbert syndrome. Phase 1 and Phase 2 (R/I patients): Resistance (suboptimal response or failure, as defined by 2013 European Leukemia Net guidelines) or intolerance (with or without suboptimal response or failure) to at least one prior tyrosine kinase inhibitor (TKI): 1. The 2013 European LeukemiaNet guidelines will be used to define suboptimal response and failure to prior TKI therapy. 2. Intolerance to prior TKI therapy will be determined by the treating investigator, but generally applies to patients who are unable to receive standard or reduced doses of a TKI due to significant drug-related toxicity and/or when the drug-related toxicity is not responding to appropriate medical management. Patients who enroll as a result of intolerance to prior TKI therapy may have any level of response to their prior therapy and still be eligible. Phase 2 (Newly Diagnosed CML patients): Able to reliably swallow whole capsules, whole tablets; or drug added to a suitable foodstuff (from capsule contents, added to either apple sauce or yogurt); or tablets and/or capsules dissolved as an oral syringe drinking solution, or tablets dissolved and administered by NG tube when needed. Phase 2 (Newly Diagnosed CML patients): Serum/urine pregnancy test (for all girls age of menarche) negative at screening. Phase 2 (Newly Diagnosed CML patients): Male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 30 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active. Phase 2 (Newly Diagnosed CML patients): Written informed consent of parent(s)/legal guardian(s) and/or patients (when applicable depending on age and local law and regulations). Phase 2 (Newly Diagnosed CML patients): Patients (including legally acceptable representative for minors where applicable) who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Phase 1 and Phase 2 (R/I patients): Age 1 and <18 years at day of attaining the informed consent. Phase 1 and Phase 2 (R/I patients): Lansky performance status 50% for patients 16 years of age, or Karnofsky scale 50% for patients >16 years of age. Phase 1 and Phase 2 (R/I patients): Adequate bone marrow function: 1. For second-line and third-line CP CML patients: a. Absolute neutrophil count >1000/mm3 (>1.0 x109/L); b. Platelets 75,000/mm3 (75 x109/L) without any platelet transfusions during the preceding 7 days. 2. For fourth-line CP and all for all AP/BP CML patients: a. Absolute neutrophil count >500/mm3 (>0.5 x109/L); b. Platelets 50,000/mm3 (50 x109/L) without any platelet transfusions during the preceding 7 days. Phase 1 and Phase 2 (R/I patients): Adequate Renal Function: Subjects must have a calculated creatinine clearance (CrCl) 60 mL/min/1.73 m2, using the Schwartz formula to estimate GFR. Phase 1 and Phase 2 (R/I patients): Adequate liver function, including: 1. AST/ALT 2.5 x upper limit normal (ULN) or 5 x ULN if attributable to disease involvement of the liver; 2. Total bilirubin 1.5 x ULN unless the patient has documented Gilbert syndrome. Phase 1 and Phase 2 (R/I patients): Recovered to Grade 0-1, or to baseline, from any acute toxicities of prior chemotherapy, immunotherapy, radiotherapy, differentiation therapy, or biologic therapy, with the exception of alopecia. Phase 1 and Phase 2 (R/I patients): Able to reliably swallow whole capsules, whole tablets; or drug added to a suitable foodstuff (from capsule contents, added to either apple sauce or yoghurt); or tablets and/or capsules dissolved in water as an oral syringe drinking solution, or tablets dissolved and administered by NG tube when needed.

Criterios de Exclusión

Phase 1 and Phase 2 (R/I patients): Diagnosis of primary Ph+ acute lymphoblastic leukemia. Phase 1 and Phase 2 (R/I patients): Pregnant and/or nursing women. Phase 1 and Phase 2 (R/I patients): Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval. Phase 1 and Phase 2 (R/I patients): In patients with AP/BP CML: leptomeningeal leukemia, defined as positive cytology on lumbar puncture (including both CNS2 and CNS3 status), or clinical symptoms or signs present. This assessment is not required for inclusion of CP CML patients. Phase 1 and Phase 2 (R/I patients): Left ventricular ejection fraction <50% or shortening fraction <28%. Phase 1 and Phase 2 (R/I patients): Recent or ongoing clinically significant gastrointestinal disorder that may interfere with the intake or absorption of the drug. Phase 1 and Phase 2 (R/I patients): Evidence of serious active or

uncontrolled bacterial, fungal or viral infection. Phase 1 and Phase 2 (R/I patients): Known history of hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness. Phase 1 and Phase 2 (R/I patients): Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study. Phase 2 (Newly Diagnosed CML patients): Diagnosis of primary Ph+ acute lymphoblastic leukemia. Phase 2 (Newly Diagnosed CML patients): Extramedullary disease only. Phase 1 and Phase 2 (R/I patients): Allogeneic stem cell transplantation within 3 months prior to bosutinib treatment. Phase 2 (Newly Diagnosed CML patients): Documented prior history of T315I or V299L BCR-ABL1 mutations (Note: BCR-ABL1 mutation testing will be performed at screening for a baseline assessment, but results are not used to determine eligibility. This exclusion criterion is based on whether there is a known history of these mutations at the time of study entry. If these mutations become evident during the study the patient will go off study). Phase 2 (Newly Diagnosed CML patients): Any prior treatment with a TKI or other anti-tumor or anti-leukemia treatment (with the exception of hydroxyurea and/or anagrelide). Phase 2 (Newly Diagnosed CML patients): Prior growth factors or biologic agents within 7 days prior to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Extramedullary disease only. Phase 2 (Newly Diagnosed CML patients): Use of strong or moderate CYP3A4 inhibitors and inducers within 7 days prior and/or concomitant to bosutinib treatment. Phase 2 (Newly Diagnosed CML patients): Use of proton pump inhibitors (Ph-modifying agents) within 7 days prior and/or concomitant to bosutinib treatment). Phase 2 (Newly Diagnosed CML patients): Hereditary bone marrow failure disorder. Phase 2 (Newly Diagnosed CML patients): Major surgery within 14 days prior to bosutinib treatment (recovery from any previous surgery should be complete before day 1). Phase 2 (Newly Diagnosed CML patients): History of clinically significant or uncontrolled cardiac disease, including: 1. History of or active congestive heart failure; 2. Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes); 3. Diagnosed or suspected congenital or acquired prolonged QT syndrome; 4. History of prolonged QTc. Phase 2 (Newly Diagnosed CML patients): Prolonged QTc (>450 msec, average of triplicate ECGs). Phase 1 and Phase 2 (R/I patients): Donor lymphocyte infusion (DLI) within 1 month prior to bosutinib treatment. Phase 2 (Newly Diagnosed CML patients): Need for medications known to prolong the QT interval. Phase 2 (Newly Diagnosed CML patients): Pregnant and/or nursing women. Phase 2 (Newly Diagnosed CML patients): Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval. Phase 2 (Newly Diagnosed CML patients): Left ventricular ejection fraction <50% or shortening fraction <28%. Phase 1 and Phase 2 (R/I patients): Documented prior history of T315I or V299L BCR-ABL1 mutations (Note: BCR-ABL1 mutation testing will be performed at screening for a baseline assessment, but results are not used to determine eligibility. This exclusion criterion is based on whether there is a known history of these mutations at the time of study entry. If these mutations become evident during the study the patient will go off study). Phase 2 (Newly Diagnosed CML patients): Recent or ongoing clinically significant gastrointestinal disorder that may interfere with the intake or absorption of the drug. Phase 2 (Newly Diagnosed CML patients): Evidence of serious active or uncontrolled bacterial, fungal or viral infection. Phase 2 (Newly Diagnosed CML patients): Known history of hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness. Phase 2 (Newly Diagnosed CML patients): Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study. Phase 1 and Phase 2 (R/I patients): Any prior treatment with a TKI within 7 days prior to starting bosutinib treatment, or other anti- tumor or anti-leukemia treatment (with the exception of hydroxyurea and/or anagrelide) within 14 days prior to start of bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Hereditary bone marrow failure disorder. Phase 1 and Phase 2 (R/I patients): Prior growth factors or biologic agents within 7 days prior to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Use of strong or moderate CYP3A4 inhibitors and inducers within 7 days prior and/or concomitant to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Use of proton pump inhibitors (Ph-modifying agents) within 7 days prior and/or concomitant to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Prior radiotherapy within 3 months prior to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Known hypersensitivity to the active substance or to any of the excipients Phase 2 (Newly Diagnosed CML patients): Known hypersensitivity to the active substance or to any of the excipients Phase 1 and Phase 2 (R/I patients): Graft-versus-host disease (GVHD) within 60 days prior to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Major surgery within 14 days prior to bosutinib treatment (recovery from any previous surgery should be complete before day 1). Phase 1 and Phase 2 (R/I patients): History of clinically significant or uncontrolled cardiac disease, including: 1. History of or active congestive heart failure; 2. Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de

pointes); 3. Diagnosed or suspected congenital or acquired prolonged QT syndrome; 4 History of prolonged QTc Phase 1 and Phase 2 (R/I patients): Prolonged QTc (>450 msec, average of triplicate ECGs). Phase 1 and Phase 2 (R/I patients): Need for medications known to prolong the QT interval.

Calendario

(Última actualización: 17/12/2025)

Autorización	Inicio de Ensayo	Inclusión Primer Paciente	Interrumpido	Reiniciado
06/11/2017	27/02/2018	04/04/2019	No aportado	No aportado

Fin de reclutamiento	Fin prematuro (España)	Fin prematuro (Global)	Fin del ensayo en España	Fin del ensayo global
28/08/2023	No aportado	No aportado	No aportado	No aportado

Promotor

Erasmus Universitair Medisch Centrum Rotterdam (Erasmus MC) Netherlands

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Contact Person

Prof. Dr. C.M. Zwaan

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trialmanagement@prinsesmaximacentrum.nl

Monetary support: N/A

Tipo de promotor: No comercial

Ceim

CEIm Hospital Infantil Universitario del Niño Jesús

Avda. Menéndez Pelayo, 65 28009 Madrid

ceic.hnjs@salud.madrid.org

Centros

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

Hospital Infantil Universitario Nino Jesus

Madrid

MADRID

Oncology

Activo (01/05/2018)

HOSPITAL INFANTIL UNIVERSITARIO NIÑO JESUS

Madrid

MADRID

Servicio de Oncología Pediátrica

Activo (03/12/2020)

HOSPITAL UNIVERSITARI VALL D'HEBRON

Barcelona

BARCELONA

Medicamentos

Bosutinib
CAPSULE
ORAL

-
Principios Activos: N/A

Experimental

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

Código ATC: L01EA04 - BOSUTINIB
Principios Activos: N/A

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FILM-COATED TABLET
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Código ATC: L01EA04 - BOSUTINIB
Principios Activos: N/A

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Código ATC: L01EA04 - BOSUTINIB
Principios Activos: N/A

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ORAL

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Principios Activos: N/A

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ORAL

Código ATC: L01EA04 - BOSUTINIB
Principios Activos: N/A

Experimental

Sin resultados

Bosutinib in pediatric CML patients

State	Type of participants	Age Ranges
End of recruitment	Incapable subjects of giving consent	Less than 18 , 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 , Phase II	60
Results	**Low level of intervention**	**Rare disease**
No results	No	Yes
Geographic coverage	**Areas of the study**	**Advanced therapy**
International multicenter	treatment, safety, effectiveness, pharmacokinetics	NO

Information

Identifier
2023-504311-32-00 (CTIS)

Protocol Code
ITCC-054/AAML1921

Transitioned 2015-002916-34

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

Investigated Disease
Chronic Myeloid Leukemia

Scientific Title
A Phase I/II study of Bosutinib in pediatric patients with newly diagnosed chronic phase or resistant/intolerant Ph+ Chronic Myeloid Leukemia, study ITCC-054/COG AAML1921

Rationale

Not provided

Main Objective

Phase 1: - To determine the Recommended Phase 2 Dose (RP2D) of bosutinib for R/I (RP2DR/I) and ND chronic phase (RP2DND) pediatric patients with CML, based on the pharmacokinetic, safety and tolerability profile of bosutinib observed at various dose levels in pediatric patients with CML who are resistant or intolerant to prior TKI therapy. Phase 2: - To assess the PK of bosutinib at the RP2DND and RP2DR/I in pediatric patients with ND or R/I Ph + CML. - To assess the population PK of bosutinib. - To assess the pooled safety and tolerability profile (based on AEs) of bosutinib in pediatric patients with ND and R/I Ph+ CML.

Primary Endpoints

Phase 1: Incidence and severity of Dose-Limiting Toxicities (DLTs) assessed during the first 28 days of treatment.
Phase 1: PK parameters of bosutinib: Maximum observed plasma concentration (Cmax), time to Cmax (Tmax), area under the plasma concentration versus time curve from time zero to the dosing interval (AUC), pre-dose concentration (Ctrough) and apparent clearance (CL/F).
Phase 2: AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v4.03), timing, seriousness, and relation to study therapy (pooled across ND and R/I CML patients and by line of therapy).
Phase 2: PK parameters of bosutinib: Maximum observed plasma concentration (Cmax), time to Cmax (Tmax), area under the plasma concentration versus time curve from time zero the dosing interval (AUC), predose concentration (Ctrough) and apparent clearance CL/F.
Phase 2: Population PK parameters of bosutinib including clearance and volume of distribution based on combined PK data from Phase 1 and Phase 2.

Temporary moments of secondary assessment

Not provided

Secondary Objective

Phase 1: To evaluate the overall safety profile during the first cycle of therapy (28 days);
Phase 1: To evaluate the safety and tolerability profile during the prolonged exposure to bosutinib;
Phase 1: To preliminary evaluate the anti-leukemic activity in pediatric patients with Philadelphia chromosome positive CML following resistance or intolerance to one or more TKIs.
Phase 2: To describe the clinical efficacy of bosutinib in pediatric patients with newly diagnosed Ph+ CML in chronic phase;
Phase 2: To describe the clinical efficacy of bosutinib in pediatric patients with Ph + CML in any phase of disease following resistance or intolerance to one or more TKIs.
Phase 2: To assess other safety parameters of bosutinib
Phase 2: To assess the relationship between the PK of bosutinib and key safety and efficacy metrics.

Secondary Endpoints

Phase 1: AEs, as characterized by type, frequency, severity (as graded using CTCAE version, v4.03), timing, seriousness, and relation to study therapy;
Phase 1: Laboratory abnormalities as characterized by type, frequency, severity and timing;
Phase 1: ECG and performance status abnormalities
Phase 1: Overall cumulative disease response: complete hematologic response (CHR), major cytogenetic response (MCyR, defined as complete cytogenetic response [CCyR] plus partial cytogenetic response [PCyR]), CCyR, major molecular response (MMR) and deep molecular response.
Phase 2: Overall cumulative disease response by the line of therapy: complete hematologic response (CHR), major cytogenetic response (MCyR, defined as complete cytogenetic response [CCyR] plus partial cytogenetic response [PCyR]), CCyR, major molecular response (MMR) and deep molecular response.
Phase 2: Time to and duration of the respective responses by line of therapy.
Phase 2: Event-free survival (EFS; including time to transformation to AP and BP CML) by line of therapy.
Phase 2: Overall survival (OS) in pediatric patients with Ph+ CML by line of therapy.
Phase 2: Laboratory abnormalities as characterized by type, frequency, severity and timing (pooled across ND and R/I CML and by line of therapy).
Phase 2: ECG and performance status abnormalities.
Phase 2: Relationships between PK parameters of bosutinib and key safety and efficacy metrics.

Temporary moments of secondary assessment

Not provided

Inclusion criteria

Phase 1 and Phase 2 (R/I patients): Cytogenetic and molecular diagnosis of Philadelphia chromosome-positive CML at either time of initial CML diagnosis or at time of study screening: 1. Cytogenetics must be performed by chromosome banding analysis (CBA) of bone marrow cell metaphases, and requires at least 20 metaphases. 2. Only if dividing marrow cells cannot be obtained, or if there is an insufficient number of metaphases, CBA can be substituted by interphase fluorescence in situ hybridization (I- FISH) of bone marrow or peripheral blood cells, using dual color dual fusion probes, that allow the detection of BCR-ABL+ nuclei; at least 200 nuclei should be counted. 3. Qualitative RT-PCR should be performed on RNA extracted from freshly collected bone marrow or peripheral blood cells. It identifies the transcript type, either e14a2 or 13a2 (also known as b3a2 and b2a2), or much more rarely e19a2, or e1a2, indicating the BCR- ABL protein weight (P210, rarely P230 or P190). Phase 1 and Phase 2 (R/I patients): Serum/urine pregnancy test (for all girls age of menarche) negative at screening. Phase 1 and Phase 2 (R/I patients): Male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 30 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active. Phase 1 and Phase 2 (R/I patients): Written informed consent of parent(s)/legal guardian(s) and/or patients (when applicable depending on age and local law and regulations). Phase 1 and Phase 2 (R/I patients): Patients (including legally acceptable representative for minors where applicable) who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Phase 2 (Newly Diagnosed CML patients): Cytogenetic and molecular diagnosis of Philadelphia chromosome-positive CML at either time of initial CML diagnosis or at time of study screening: 1. Cytogenetics must be performed by chromosome banding analysis (CBA) of bone marrow cell metaphases, and requires at least 20 metaphases. 2. Only if dividing marrow cells cannot be obtained, or if there is an insufficient number of metaphases, CBA can be substituted by interphase fluorescence in situ hybridization (I- FISH) of bone marrow or peripheral blood cells, using dual color dual fusion probes, that allow the detection of BCR-ABL+ nuclei; at least 200 nuclei should be counted. 3. Qualitative RT-PCR should be performed on RNA extracted from freshly collected bone marrow or peripheral blood cells. It identifies the transcript type, either e14a2 or e13a2 (also known as b3a2 and b2a2), or much more rarely

e19a2, or e1a2, indicating the BCR- ABL protein weight (P210, rarely P230 or P190). Phase 2 (Newly Diagnosed CML patients): Newly diagnosed CP Ph+ CML of 6 months (from initial diagnosis) without any previous TKI treatment (with the exception of hydroxyurea and/or anagrelide) for CML. Phase 2 (Newly Diagnosed CML patients): Age 1 and <18 years at day of attaining the informed consent. Phase 2 (Newly Diagnosed CML patients): Lansky performance status 50% for patients 16 years of age, or Karnofsky scale 50% for patients >16 years of age. Phase 2 (Newly Diagnosed CML patients): Adequate Renal Function: Subjects must have a calculated creatinine clearance (CrCl) 60 mL/min/1.73 m2, using the Schwartz formula to estimate GFR. Phase 2 (Newly Diagnosed CML patients): Adequate liver function, including: 1. AST/ALT 2.5 x upper limit normal (ULN) or 5 x ULN if attributable to disease involvement of the liver; 2. Total bilirubin 1.5 x ULN unless the patient has documented Gilbert syndrome. Phase 1 and Phase 2 (R/I patients): Resistance (suboptimal response or failure, as defined by 2013 European Leukemia Net guidelines) or intolerance (with or without suboptimal response or failure) to at least one prior tyrosine kinase inhibitor (TKI): 1. The 2013 European LeukemiaNet guidelines will be used to define suboptimal response and failure to prior TKI therapy. 2. Intolerance to prior TKI therapy will be determined by the treating investigator, but generally applies to patients who are unable to receive standard or reduced doses of a TKI due to significant drug-related toxicity and/or when the drug-related toxicity is not responding to appropriate medical management. Patients who enroll as a result of intolerance to prior TKI therapy may have any level of response to their prior therapy and still be eligible. Phase 2 (Newly Diagnosed CML patients): Able to reliably swallow whole capsules, whole tablets; or drug added to a suitable foodstuff (from capsule contents, added to either apple sauce or yogurt); or tablets and/or capsules dissolved as an oral syringe drinking solution, or tablets dissolved and administered by NG tube when needed. Phase 2 (Newly Diagnosed CML patients): Serum/urine pregnancy test (for all girls age of menarche) negative at screening. Phase 2 (Newly Diagnosed CML patients): Male and female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 30 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active. Phase 2 (Newly Diagnosed CML patients): Written informed consent of parent(s)/legal guardian(s) and/or patients (when applicable depending on age and local law and regulations). Phase 2 (Newly Diagnosed CML patients): Patients (including legally acceptable representative for minors where applicable) who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Phase 1 and Phase 2 (R/I patients): Age 1 and <18 years at day of attaining the informed consent. Phase 1 and Phase 2 (R/I patients): Lansky performance status 50% for patients 16 years of age, or Karnofsky scale 50% for patients >16 years of age. Phase 1 and Phase 2 (R/I patients): Adequate bone marrow function: 1. For second-line and third-line CP CML patients: a. Absolute neutrophil count >1000/mm3 (>1.0 x109/L); b. Platelets 75,000/mm3 (75 x109/L) without any platelet transfusions during the preceding 7 days. 2. For fourth-line CP and all for all AP/BP CML patients: a. Absolute neutrophil count >500/mm3 (>0.5 x109/L); b. Platelets 50,000/mm3 (50 x109/L) without any platelet transfusions during the preceding 7 days. Phase 1 and Phase 2 (R/I patients): Adequate Renal Function: Subjects must have a calculated creatinine clearance (CrCl) 60 mL/min/1.73 m2, using the Schwartz formula to estimate GFR. Phase 1 and Phase 2 (R/I patients): Adequate liver function, including: 1. AST/ALT 2.5 x upper limit normal (ULN) or 5 x ULN if attributable to disease involvement of the liver; 2. Total bilirubin 1.5 x ULN unless the patient has documented Gilbert syndrome. Phase 1 and Phase 2 (R/I patients): Recovered to Grade 0-1, or to baseline, from any acute toxicities of prior chemotherapy, immunotherapy, radiotherapy, differentiation therapy, or biologic therapy, with the exception of alopecia. Phase 1 and Phase 2 (R/I patients): Able to reliably swallow whole capsules, whole tablets; or drug added to a suitable foodstuff (from capsule contents, added to either apple sauce or yoghurt); or tablets and/or capsules dissolved in water as an oral syringe drinking solution, or tablets dissolved and administered by NG tube when needed.

Exclusion criteria

Phase 1 and Phase 2 (R/I patients): Diagnosis of primary Ph+ acute lymphoblastic leukemia. Phase 1 and Phase 2 (R/I patients): Pregnant and/or nursing women. Phase 1 and Phase 2 (R/I patients): Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval. Phase 1 and Phase 2 (R/I patients): In patients with AP/BP CML: leptomeningeal leukemia, defined as positive cytology on lumbar puncture (including both CNS2 and CNS3 status), or clinical symptoms or signs present. This assessment is not required for inclusion of CP CML patients. Phase 1 and Phase 2 (R/I patients): Left ventricular ejection fraction <50% or shortening fraction <28%. Phase 1 and Phase 2 (R/I patients): Recent or ongoing clinically significant gastrointestinal disorder that may interfere with the intake or absorption of the drug. Phase 1 and Phase 2 (R/I patients): Evidence of serious active or

uncontrolled bacterial, fungal or viral infection. Phase 1 and Phase 2 (R/I patients): Known history of hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness. Phase 1 and Phase 2 (R/I patients): Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study. Phase 2 (Newly Diagnosed CML patients): Diagnosis of primary Ph+ acute lymphoblastic leukemia. Phase 2 (Newly Diagnosed CML patients): Extramedullary disease only. Phase 1 and Phase 2 (R/I patients): Allogeneic stem cell transplantation within 3 months prior to bosutinib treatment. Phase 2 (Newly Diagnosed CML patients): Documented prior history of T315I or V299L BCR-ABL1 mutations (Note: BCR-ABL1 mutation testing will be performed at screening for a baseline assessment, but results are not used to determine eligibility. This exclusion criterion is based on whether there is a known history of these mutations at the time of study entry. If these mutations become evident during the study the patient will go off study). Phase 2 (Newly Diagnosed CML patients): Any prior treatment with a TKI or other anti-tumor or anti-leukemia treatment (with the exception of hydroxyurea and/or anagrelide). Phase 2 (Newly Diagnosed CML patients): Prior growth factors or biologic agents within 7 days prior to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Extramedullary disease only. Phase 2 (Newly Diagnosed CML patients): Use of strong or moderate CYP3A4 inhibitors and inducers within 7 days prior and/or concomitant to bosutinib treatment. Phase 2 (Newly Diagnosed CML patients): Use of proton pump inhibitors (Ph-modifying agents) within 7 days prior and/or concomitant to bosutinib treatment). Phase 2 (Newly Diagnosed CML patients): Hereditary bone marrow failure disorder. Phase 2 (Newly Diagnosed CML patients): Major surgery within 14 days prior to bosutinib treatment (recovery from any previous surgery should be complete before day 1). Phase 2 (Newly Diagnosed CML patients): History of clinically significant or uncontrolled cardiac disease, including: 1. History of or active congestive heart failure; 2. Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes); 3. Diagnosed or suspected congenital or acquired prolonged QT syndrome; 4. History of prolonged QTc. Phase 2 (Newly Diagnosed CML patients): Prolonged QTc (>450 msec, average of triplicate ECGs). Phase 1 and Phase 2 (R/I patients): Donor lymphocyte infusion (DLI) within 1 month prior to bosutinib treatment. Phase 2 (Newly Diagnosed CML patients): Need for medications known to prolong the QT interval. Phase 2 (Newly Diagnosed CML patients): Pregnant and/or nursing women. Phase 2 (Newly Diagnosed CML patients): Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval. Phase 2 (Newly Diagnosed CML patients): Left ventricular ejection fraction <50% or shortening fraction <28%. Phase 1 and Phase 2 (R/I patients): Documented prior history of T315I or V299L BCR-ABL1 mutations (Note: BCR-ABL1 mutation testing will be performed at screening for a baseline assessment, but results are not used to determine eligibility. This exclusion criterion is based on whether there is a known history of these mutations at the time of study entry. If these mutations become evident during the study the patient will go off study). Phase 2 (Newly Diagnosed CML patients): Recent or ongoing clinically significant gastrointestinal disorder that may interfere with the intake or absorption of the drug. Phase 2 (Newly Diagnosed CML patients): Evidence of serious active or uncontrolled bacterial, fungal or viral infection. Phase 2 (Newly Diagnosed CML patients): Known history of hepatitis B (HBV), hepatitis C (HCV), or human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness. Phase 2 (Newly Diagnosed CML patients): Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study. Phase 1 and Phase 2 (R/I patients): Any prior treatment with a TKI within 7 days prior to starting bosutinib treatment, or other anti- tumor or anti-leukemia treatment (with the exception of hydroxyurea and/or anagrelide) within 14 days prior to start of bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Hereditary bone marrow failure disorder. Phase 1 and Phase 2 (R/I patients): Prior growth factors or biologic agents within 7 days prior to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Use of strong or moderate CYP3A4 inhibitors and inducers within 7 days prior and/or concomitant to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Use of proton pump inhibitors (Ph-modifying agents) within 7 days prior and/or concomitant to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Prior radiotherapy within 3 months prior to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Known hypersensitivity to the active substance or to any of the excipients Phase 2 (Newly Diagnosed CML patients): Known hypersensitivity to the active substance or to any of the excipients Phase 1 and Phase 2 (R/I patients): Graft-versus-host disease (GVHD) within 60 days prior to bosutinib treatment. Phase 1 and Phase 2 (R/I patients): Major surgery within 14 days prior to bosutinib treatment (recovery from any previous surgery should be complete before day 1). Phase 1 and Phase 2 (R/I patients): History of clinically significant or uncontrolled cardiac disease, including: 1. History of or active congestive heart failure; 2. Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de

pointes); 3. Diagnosed or suspected congenital or acquired prolonged QT syndrome; 4 History of prolonged QTc Phase 1 and Phase 2 (R/I patients): Prolonged QTc (>450 msec, average of triplicate ECGs). Phase 1 and Phase 2 (R/I patients): Need for medications known to prolong the QT interval.

Calendar

(Last Update: 17/12/2025)

Authorization	Start of Trial	First patient inclusion	Halted	Restarted
06/11/2017	27/02/2018	04/04/2019	Not aported	Not aported

End of recruitment	Premature end (Spain)	Premature End (Global)	Trial end (Spain)	Trial end (Global)
28/08/2023	Not aported	Not aported	Not aported	Not aported

Sponsor

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Dr. Molewaterplein 40

Contact Person

Prof. Dr. C.M. Zwaan

+31889725206

trialmanagement@prinsesmaximacentrum.nl

Monetary support: N/A

Sponsor type: No commercial

Ceim

CEIm Hospital Infantil Universitario del Niño Jesús

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Sites

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

Hospital Infantil Universitario Nino Jesus

Madrid

MADRID

Oncology

Active (01/05/2018)

HOSPITAL INFANTIL UNIVERSITARIO NIÑO JESUS

Madrid

MADRID

Servicio de Oncología Pediátrica

Active (03/12/2020)

HOSPITAL UNIVERSITARI VALL D'HEBRON

Barcelona

BARCELONA

Medication

Bosutinib
CAPSULE
ORAL

-

Active Principles: N/A

Experimental

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

ATC code: L01EA04 - BOSUTINIB
Active Principles: N/A

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Active Principles: N/A

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ORAL

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Active Principles: N/A

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ORAL

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ORAL

ATC code: L01EA04 - BOSUTINIB
Active Principles: N/A

Experimental

No results