An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Ponatinib for the Treatment of Recurrent or Refractory Leukemias or Solid Tumors in Pediatric Participants.

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This study has been transitioned to CTIS with ID 2023-509699-41-00 check the CTIS register for the current data. Primary objectives:Phase 1: To determine the MTD and/or RP2D of oral ponatinib administered QD in pediatric participants with selected...

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

Summary

ID

NL-OMON54589

Source
ToetsingOnline

Brief title
INCB 84344-102

Condition

- Other condition
- Leukaemias
- Leukaemias

Synonym
Recurrent or Refractory Leukemias; Solid Tumors

Health condition

overige neoplasmata, benigne, maligne en site niet gespecificeerd

Research involving
Human

Sponsors and support

Primary sponsor: Incyte Biosciences International Sarl
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Children, Recurrent or Refractory Leukemias, Solid Tumors

Outcome measures

Primary outcome

Phase 1: Determination of DLTs during the DLT evaluation period (first 28 days

of treatment).

Phase 2:

- Group A (CP-CML): MCyR, defined as CCyR or PCyR by 12 months, assessed by

conventional cytogenetics or FISH.

- Group B (Other Tumors):

Hematologic malignancies:

• BCR-ABL-positive leukemias (CML in AP or BP; Ph+ ALL):

* MaHR or MMR assessed by q-PCR by 3 months.

• Other leukemias:

* CR.

* CRi assessed by conventional cytogenetics, FISH, or q PCR.

• Lymphoma:

* CR according to Lugano criteria (Cheson et al 2014) based on CT or MRI (or PET).

Solid tumors:

• ORR, defined as the percentage of participants having CR or PR, as determined by investigator assessment of radiographic disease per tumors per RANO for CNS tumors or RECIST v1.1 for other solid tumors based on CT or MRI (or PET).

Secondary outcome

Phase 1:

- Frequency and severity of AEs and SAEs.

- Changes in vital signs and clinical evaluations.

- Changes in clinical laboratory blood samples.

- PK parameters: Tmax, AUCss, 0-24, t*, CLss/F, Vz/F.

Phase 2:

Group A (CP-CML):

• CHR at 6 months.

• CCyR at 12 months.

• MMR at 12 months.

• TTR, defined as the interval from the date of the first dose of study treatment to first response.

• DOR, defined as the interval between the first assessment at which the criteria for response are met until the criteria for progression are met.

• PFS, defined as defined as the interval from the date of the first dose of study treatment until the date of progression of disease or death from any

cause, whichever is earlier.

• OS, defined as the interval from the date of first dose of study treatment until death from any cause.

Group B (Other Tumors):

Hematologic malignancies:

• BCR-ABL-positive leukemias (CML in AP or BP; Ph+ ALL):

* MHR or MMR by 3 months.

• Other leukemias:

* CR.

* CRi, as assessed by conventional cytogenetics, FISH, or q-PCR.

• Lymphoma:

* CR according to Lugano criteria (Cheson et al 2014) based on CT or MRI (or PET).

Solid tumors:

• ORR, defined as the percentage of participants having CR or PR, as determined by investigator assessment of radiographic disease per tumors per RANO for CNS tumors or RECIST v1.1 for other solid tumors based on CT or MRI (or PET).

• OS, defined as the interval between the date of the first dose of study treatment until the date of death from any cause.

• DOR, defined as the interval between the first assessment at which the criteria for response are met until the criteria for progression are met.

• PFS, defined as the interval from the date of the first dose of study treatment until the date of progression of disease or death from any cause,

whichever is earlier.

Study description

Background summary

Please refer to the research protocol, section 2.2. Study Rationale.
Ponatinib is approved for the treatment of adult patients with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Just like in adults, some of the recurrent or refractory leukemias and solid tumors may be resistant to the currently approved medicines for treatment of these diseases in children. Therefore, the sponsor will investigate if ponatinib also works in children (aged 1 to <18 yrs) with these diseases.

Study objective

This study has been transitioned to CTIS with ID 2023-509699-41-00 check the CTIS register for the current data.

Primary objectives:
Phase 1: To determine the MTD and/or RP2D of oral ponatinib administered QD in pediatric participants with selected advanced hematologic malignancies or solid tumors.
Phase 2
- Group A (CP-CML): To determine the efficacy of oral ponatinib administered QD in pediatric participants with CP CML who are resistant or intolerant to at least 1 prior BCR-ABL-targeted TKI therapy or who have the T315I mutation.
- Group B (Other Tumors): To determine the efficacy of oral ponatinib administered QD in pediatric participants with other selected advanced hematologic malignancies or solid tumors.

Major/Key secondary objectives:
Phase 1:
- To examine the safety and tolerability of ponatinib in pediatric participants with selected advanced hematologic malignancies or solid tumors.
- To evaluate the PK properties of ponatinib in pediatric participants.
Phase 2
- Group A (CP-CML):
• To determine the antileukemia activity of ponatinib participants with CP-CML.
• To determine the cytogenetics and molecular response.
- Group B (Other Tumors): To determine anticancer activity of ponatinib in pediatric participants with selected advanced hematologic malignancies or solid

tumors.

Study design

This is an open-label, single-arm, Phase 1/2 study of single-agent ponatinib using a rolling-six design.
The study will be run in 2 parts: Phase 1 (dose escalation) and Phase 2 (expansion).
It will be conducted in a staggered approach in the following 3 cohorts: >= 12 to < 18 years old (Cohort 1); >= 6 to < 12 years old (Cohort 2); >= 1 to < 6 years old (Cohort 3), starting with Cohort 1 in Phase 1. Phase 2 could be initiated with the Cohort 1 age group once RP2D in this cohort is defined.

Intervention

The children will be treated with ponatinib in continuous 28-day cycles.

Study burden and risks

This is a brief list of the most commonly seen side effects seen with Iclusig® (ponatinib). A complete list can be found in appendix C of the informed consent form.
• Pancreatitis, increased amylase and lipase
• Myelosuppression (thrombocytopenia, neutropenia, anemia)
• Infections
• Skin reactions (rash, erythema, dry skin, acneiform dermatitis, exfoliative rash)
• Hepatotoxicity
• Hypertension
• Edema and fluid retention
• Cardiac failure/Left Ventricular dysfunction
• Vascular Occlusive events comprising:
- Arterial Occlusive Events (cardiac/cerebral/peripheral vascular/retinal arterial occlusive events)
- Venous Thrombotic/Embolic events (Retinal vein thrombotic events and vision loss)
• Bleeding
The study medication may also have side effects that are still unknown.

Other risks:
- Blood draws/blood tests: Momentary discomfort, soreness, bruising, and in rare cases, infection at the draw site or excess bleeding; rarely light headedness or fainting. Approximate total amount of blood drawn of the course of the study for the phase 1: 220 ml (15 tablespoons) for 3 cycles and follow-up visits, approximately 270 ml (18 tablespoons) for the phase 2 for 3 cycles (average amount for blood donation is 16 ounces- 480 mL)

- Bone marrow aspirate/biopsy: Procedure risks (depending on location): Pain, bleeding, bruising, dizziness, scarring, and a small risk of infection.
Side effects from numbing medication: Mild irritation where medication is applied. There may be additional risks depending on where your biopsy is performed. Your/your child*s Study Doctor will discuss these additional risks with you.
- CT scan: Contrast material risks: Allergic reactions (from itching/rash to allergic reaction (from mild itching/rash to severe difficulty breathing, shock, rarely death), and kidney problems (if dehydration or poor kidney function).
- PET scan: Contrast material risks: Might cause a major allergic reaction.
- MRI: Enclosed space risks: Feel claustrophobic (fear of being closed in), nervousness, sweating, and loud sound.
An MRI cannot be performed if you have metal in your body (eg, pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, some implanted metallic or electrical devices, or plates). You/your child need/s to tell his/her Study Doctor or Study staff if your child has metal in his/her body.
- DEXA scan: Uses a very low level of X-ray radiation on limited bone parts.
- ECG: Sticky pads possible risks: Rash and minor irritation of the skin.
- other precautons: Other drugs or medication prescribed by other doctors may affect your/your child*s response to the Study Drug. Therefore, it is very important that you/your child inform the doctor in charge of the study about all the drugs your child is taking at the time of joining the study and about any medication your child may need to start taking during his/her participation in the study. This also includes products of natural or herbal origin.
No other drugs or medications should be started before approval from the Study Doctor.
Based on the studies conducted on both animals and humans, the drugs used in this study may cause some side effects, which depend on the treatment administered. It is also possible that problems or new side effects may occur. You/your child will be informed of any changes in the way the study will be conducted. You/your child will be informed about new risks or side effects. This information could influence your decision to continue participating in the study.

Contacts

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Scientific

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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

1. Histologically or cytologically confirmed diagnosis of the following malignancies:
a. Phase 1:
* CP-CML, BP-CML, AP-CML (relapse defined in Appendix G).
* ALL.
* AML.
* Other leukemias.
* Lymphoma.
* Any other tumors, including tumors of the CNS, for which standard therapy is not available or is not indicated.
b. Phase 2, Group A with CP-CML:
* CP-CML (defined in Appendix G) at the time of study entry and must be resistant to or intolerant of at least 1 prior BCR-ABL-targeted TKI therapy or have the T315I kinase domain mutation or be in "warning" response status. Warning response status must a) be confirmed by at least 2 assessments performed at least 1 month apart and b) justify the change of treatment by comorbidities and tolerability.
* Must have 1 bone marrow aspirate with documentation of BCR-ABL translocation by conventional cytogenetics, metaphase FISH, or q-PCR performed within 42 days before the first dose of ponatinib.

c. Phase 2, Group B with other leukemias or solid tumors:
* ALL.
* AML.
* Other leukemias.
* Lymphoma.
* Any other tumors, including tumors of the CNS, with mutations of RET, FLT3, KIT, FGFR, PDGFR, TIE2 VEGFR, or any other mutations where ponatinib may have biological activity (eg. EPH receptors and SRC families of kinases) as assessed on fresh or archived tumor tissue.
* Participants with solid tumors or with lymphoma must have measurable disease by CT or MRI based on RECIST v1.1 or the Lugano lymphoma guidelines (Cheson et al 2014) as determined by site radiology.
2. Prior therapies as follows:
a. Phase 1:
* Participants with CML who are resistant to or intolerant of (as defined Appendix G) to at least 1 prior BCR-ABL-targeted TKI therapy.
* Participants with ALL who have failed all available or indicated therapies, which may have included 1 prior BCR-ABL-targeted TKI therapy.
* Participants with AML or other leukemias who have progressed on or after at least 1 prior induction attempt (for France only) or for whom no effective standard therapy is available or indicated (for other countries).
* Participants with solid tumors (including tumors of the CNS) or lymphomas who have progressed despite standard therapy or for whom no effective standard therapy is available or indicated.
b. Phase 2, Group A with CP-CML:
* Participants who are resistant to or intolerant of at least 1 prior BCR-ABL-targeted TKI therapy.
c. Phase 2, Group B with other leukemias or solid tumors:
* Participants with ALL who have progressed on or after all available or indicated therapies, which must have included 1 prior BCR-ABL-targeted TKI therapy (exception for participants with T315I mutation) or are in warning status.
* Participants with AML or other leukemias who have failed at least 1 prior induction attempt (for France only) or for whom no effective standard therapy is available or indicated (for other countries).
* Participants with solid tumors (including tumors of the CNS) or lymphomas who progressed despite standard therapy or for whom no effective standard therapy is available or indicated.
3. Must have a parent or legal guardian able to comprehend and willing to sign a written ICF for the study and assent (when appropriate) according to institutional standards and to comply with all study visits and procedures.
4. Male and female participants >= 1 to < 18 years old, inclusive, at the time of signing the informed consent.
5. Karnofsky performance status >= 40% for participants >= 16 years old or Lansky Play Scale >= 40 for pediatric participants < 16 years old.
6. Participants must have recovered to < Grade 2 per the NCI CTCAE v5.0 or to baseline from any non-hematologic toxicities (except alopecia) due to previous

therapy.

Exclusion criteria

2. Prior therapies:
a. Participants with BP-CML, ALL, or AML who have received any of the following:
* Corticosteroids or hydroxyurea within 24 hours before the first dose of ponatinib.
* Vincristine within 7 days before the first dose of ponatinib.
* Other chemotherapy (excluding intrathecal chemotherapy) within 14 days before the first dose of ponatinib.
b. Participants (except the BP-CML, ALL, and AML participants described above) who:
* Have had cytotoxic chemotherapy or radiotherapy within 21 days (or 42 days for nitrosoureas or mitomycin C) before the first dose of ponatinib.
c. Prior radiation therapy or radio-isotope therapy before or radio-isotope therapy within 6 weeks before the first dose of ponatinib except local radiotherapy for palliative indication within 14 days before the first dose of ponatinib. For CNS, at least 90 days must have passed if the participant received prior total body irradiation or craniospinal or cranial radiotherapy.
d. Autologous or allogeneic stem cell transplant < 3 months before the first dose of ponatinib.
e. Major surgery within 14 days before the first dose of ponatinib.
Note: Minor surgical procedures, such as central venous catheter placement or bone marrow aspirate/biopsy, are permitted.
f. Inadequate recovery and/or complications from a major surgery before starting therapy.
g. Prior treatment with any of the following:
* Immunosuppressive therapy (including post stem cell transplant regimens) within 14 days before the first dose of ponatinib.
* Any targeted cancer therapy (including TKIs) within 7 days before the first dose of ponatinib.
* Any other investigational anticancer agents within 30 days or 5 half-lives, whichever is longer, before randomization.
* Any biotherapeutic (including monoclonal antibody-directed anticancer therapy within 5 half-lives or 30 days whichever is shorter, before of the first dose of ponatinib.
Note: Supportive care medications for CNS edema (eg, stable doses of corticosteroids or bevacizumab) are permitted.
* Any chimeric antigen receptor therapy within 28 days before the first dose of ponatinib
* Ponatinib.
3. Participants with laboratory values at screening defined as follows:
Solid tumors
a Platelets <= 75 × 109/L

b Hemoglobin <= 8 g/L
c ANC <= 1 × 109/L
Hepatic
d ALT >= 5 × ULN for age (unless related to leukemic involvement)
e AST >= 5 × ULN for age (unless related to leukemic involvement)
f Direct bilirubin >= 1.5 × ULN for age
Pancreatic
g Amylase > 2 × ULN for age
h Lipase > 2 × ULN for age
Renal
i Serum creatinine OR Serum creatinine clearance > ULN for age based on age/gender chart below:
Age (years) Maximum Serum Creatinine (mg/dL)
Male Female
1 to < 2 0.6 0.6
2 to < 6 0.8 0.8
6 to < 10 1 1
10 to < 13 1.2 1.2
13 to < 16 1.5 1.4
>= 16 1.7 1.4
OR Calculated creatinine clearance of radioisotope glomerular filtration rate < 70 mL/min/1.73 m2
Coagulation
j INR or PT > 1.5 × ULN for age
k aPTT > 1.5 × ULN for age
Lipids
l Triglycerides >= 450 mg/dL
4. Significant concurrent, uncontrolled medical condition, including but not limited to the following:
a. Pancreatic: clinical, radiological, or laboratory evidence of pancreatitis.
b. Cardiac:
* SF < 27% by ECHO, OR EF < 50% by MUGA.
* Abnormal QTcF on screening ECG, defined as QTcF of >= 450 ms.
* Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute MI within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV CHF (see Appendix O), and arrhythmia requiring therapy unless approved by the medical monitor/sponsor.
* Uncontrolled hypertension.
* Currently taking drug(s) that are known to have a risk of causing prolonged QTc or TdP unless the drug(s) can be changed to acceptable alternatives (ie, an alternate class of agents that do not affect the cardiac conduction system), or the participant can safely discontinue the drug(s).
c. Cerebral:
* Participants with solid tumors with intracranial metastasis OR participants with active CNS leukemia (ie, CNS-2 status [< 5/µL WBCs and cytospin positive for blasts, or >= 5 /µL WBCs but negative by Steinherz/Bleyer algorithm

(equation used for traumatic lumbar punctures), disseminated leptomeningeal disease, or CNS chloroma.
* Pre-existing significant CNS pathology including history of severe brain injury, dementia, cerebellar disease, organic brain syndrome, psychosis, coordination/movement disorder, or autoimmune disease with CNS involvement.
* History of cerebrovascular ischemia/hemorrhage with residual deficits.
Note: Participants with a history of cerebrovascular ischemia/hemorrhage remain eligible provided all neurologic deficits have resolved.
* Uncontrolled seizure disorder.
d. Coagulation:
* Significant bleeding disorder or thrombophilia unrelated to the underlying malignancy indication for study participation.
e. Gastrointestinal:
* Gastrointestinal disorders, such as malabsorption syndrome or any other illness that could affect oral absorption.
f. Genetic:
* Participants with DNA fragility syndromes, such as Fanconi anemia and Bloom syndrome.
* Participants with Down syndrome.
5. Participants with any active >= Grade 2 graft versus host disease.
6. Chronic or current active uncontrolled infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment.
7. Active HBV or HCV infection that requires treatment or at risk for HBV reactivation. Hepatitis B virus DNA and HCV RNA must be undetectable upon testing. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or
anti-hepatitis B core antibody positive.
8. Known HIV infection.
9. Current use of prohibited medication (see Section 6.7.2).
10. Known hypersensitivity or severe reaction to ponatinib or excipients of ponatinib.
11. Receipt of live (including attenuated) vaccines or anticipation of need for such vaccines during the study.
12. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
13. Females who are pregnant or lactating.
14. Any condition or illness that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
15. Inability of the participant (or parent, guardian, or legally authorized representative) to comprehend the ICF or unwillingness to sign the ICF.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-06-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Iclusig
Generic name:	ponatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-09-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-01-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-04-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-06-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-509699-41-00
EudraCT	EUCTR2018-004878-99-NL
ClinicalTrials.gov	NCT03934372
CCMO	NL70716.041.19