A Phase 1/2 Study of the Oral TRK Inhibitor larotrectinib in Pediatric patients with Advanced Solid or Primary Central Nervous System Tumors

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This study has been transitioned to CTIS with ID 2022-502668-20-00 check the CTIS register for the current data. PHASE 1 OBJECTIVES:Primary:To determine the safety of oral larotrectinib , including dose-limiting toxicity (DLT), in pediatric patients...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54602

Source
ToetsingOnline

Brief title
SCOUT

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Nervous system neoplasms malignant and unspecified NEC

Synonym
Advanced Solid or Primary Central Nervous System Tumors

Research involving
Human

Sponsors and support

Primary sponsor: Bayer Consumer Care AG
Source(s) of monetary or material Support: Bayer Consumer Care AG

Intervention

Keyword: Cancer, Central Nervous System, Larotrectinib, Pediatric

Outcome measures

Primary outcome

Phase 1:

DLT (dose-limiting toxicity) of larotrectinib

Phase 2:

total ORR (overall response rate), total confirmed response compared to the complete response (CR) or partial response (PR), depending on RECIST 1.1 or the RANO-criteria and INRC criteria.

Secondary outcome

Phase 1:

- To characterize the pharmacokinetic (PK) properties of larotrectinib in pediatric patients with advanced solid or primary CNS tumors
- To identify the maximum tolerated dose (MTD) and/or the appropriate dose of larotrectinib for further clinical investigation in this patient population
- To describe the antitumor activity of larotrectinib in pediatric patients with advanced solid or primary CNS tumors
- To describe pain and health related quality of life (HRQOL) in pediatric patients with advanced solid or primary CNS tumors treated with larotrectinib

Phase 2:

To determine the ORR based on the treating Investigator*s response assessment using RANO for primary CNS tumor criteria, and INRC for neuroblastoma and RECIST 1.1 for all other solid tumors.

• To evaluate the duration of response (DOR) in patients with best overall response of CR or PR as determined by 1) an independent radiology review committee and 2) the treating Investigator

• To estimate the proportion of patients that have any tumor regression as a best response

• To evaluate the duration of progression-free survival (PFS) following initiation of larotrectinib

• To evaluate the duration of overall survival (OS) following initiation of larotrectinib

• To assess the safety profile and tolerability of larotrectinib

• To evaluate the clinical benefit rate (CBR) based on the proportion of patients with best overall response of CR, PR, or stable disease lasting 16 or more weeks following initiation of larotrectinib as determined by 1) an independent radiology review committee and 2) the treating Investigator

Study description

Background summary

Infantile fibrosarcoma is a rare tumor diagnosis which normally has good prognosis, is surgically resectable and/or chemosensitive, and has low-risk of metastatic disease. For disease which is amendable to surgery, and specifically extremity disease, the rate of amputations may exceed 50%. There

is an even rarer subset of IF which is metastatic, is not chemosensitive, and has a poorer prognosis. The extent of this group is not well known, due to the rarity of the tumor itself and a potential publication bias against reporting negative treatment outcomes. However, previous research suggests there is a group of patients in whom normal therapy does not work. The ETV6-NTRK3 gene-fusion has been routinely implicated in the diagnosis of IFS. The ETV6-NTRK3 fusion is the archetypical cancer-driver mutation by driving the growth of tumors via constitutive activation in its tyrosine kinase activity, thereby inducing cancer cell proliferation and initiating cancer-related downstream signaling pathways. Recent research into the molecular mechanism of pediatrics tumors has identified inhibition of activated RTKs as a potential therapeutic intervention for the targeted treatment of these cancers.

Study objective

This study has been transitioned to CTIS with ID 2022-502668-20-00 check the CTIS register for the current data.

PHASE 1 OBJECTIVES:
Primary:
To determine the safety of oral larotrectinib , including dose-limiting toxicity (DLT), in pediatric patients with advanced solid or primary central nervous system (CNS) tumors.

PHASE 2 OBJECTIVES:
Primary Objective:
To determine the overall response rate (ORR) as determined by an independent radiology review committee and measured by the proportion of patients with best overall confirmed response of complete response (CR) or partial response (PR) according to the appropriate tumor response criteria following treatment with larotrectinib in pediatric patients with an advanced cancer harboring a fusion involving NTRK1, NTRK2, or NTRK3 (collectively referred to as NTRK fusions) fusions.

Study design

Phase 1 Dose Escalation
This part of the study is a multicenter, open-label, Phase 1 study in pediatric patients with advanced solid or
primary CNS tumors. Larotrectinib will be administered orally (PO) twice daily (BID), with the dose
adjusted by body surface area (BSA).

Phase 1 Expansion Cohort
To confirm that a safe level of drug exposure has been established, up to 18 additional patients may be

enrolled in an expansion cohort, following the formal dose escalation phase of the study. With the approval
from the SRC, one or more doses may be explored in this expansion cohort. The expansion cohort may
accrue in parallel to the Phase 2 portion of the study (e.g., the expansion cohort does not need to complete
accrual before the Phase 2 portion of the study opens for accrual).

Phase 2 Efficacy Cohorts
This part of the study is a Phase 2 expansion which will include 3 cohorts of subjects with tumors bearing NTRK fusions (infantile fibrosarcoma, other extra-cranial solid tumors with NTRK gene fusions and primary CNS tumors). Patients with infantile fibrosarcoma do not require any additional molecular testing for eligibility to enroll. Patients with infantile fibrosarcoma, CMN or SBC will require a documented ETV6 rearrangement (or NTRK3 rearrangement after discussion with the Sponsor) by FISH or RT-PCR or a documented NTRK fusion by e.g. NGS for eligibility to enrol. Patients with solid tumors with an NTRK fusion will be locally identified through molecular assays as routinely performed at Clinical Laboratory Improvement Amendments of 1988 (CLIA) or other similarly certified laboratories. If CLIA or similar certification of the laboratory performing the molecular assay is not confirmed at the time of consent patients may be included after discussion with the Sponsor. Patients are required to have RECIST 1.1, or INRC measurable disease to be enrolled. Larotrectinib is administered in oral capsule or liquid formulation at the recommended Phase 2 dose. Each cycle consists of 28 days.

Intervention

Phase 1:
Larotrectinib will be administered orally (PO) twice daily (BID), with the dose adjusted by body surface area (BSA).

Phase 2:
Larotrectinib is administered in oral capsule or liquid formulation.

The recommended Phase 2 dose (100mg/m2 BID, not to exceed a dose of 100mg BID) was declared on 13-Apr-2017. With protocol amendment 8.0, the age of enrollment is being lowered to infants aged from birth and older. In those patients enrolled aged between birth and 1 month, a dose 50% of the recommended Phase 2 dose, converted to 3mg/kg, will be used. If no DLTs are reported during Cycle 1, patients will automatically be increased to the recommended Phase 2 dose on Cycle 2 Day 1.

At least 7 of the patients enrolled will receive the new age-appropriate, improved oral solution formulation.

Study burden and risks

Risks: possible side effects of the study drug and study procedures
Burden: Blood draws, filling in questionnaires, radiation load

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

Inclusion Criteria

1. Phase 1: Birth through 21 years of age at C1D1 with a locally advanced or metastatic solid tumor or primary CNS tumor that has relapsed, progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy exists,
or:
Infants from birth and older with a diagnosis of malignancy and with a documented NTRK fusion that has progressed or was nonresponsive to available therapies, and for which no standard or available curative therapy exists.
or:
Patients with locally advanced infantile fibrosarcoma who would require, in the opinion of the Investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection
The Phase 1 dose escalation cohorts are closed to enrollment.
Phase 1 dose expansion: In addition to the above stated Inclusion Criteria, patients eligible for enrollment onto this cohort must have a malignancy with a documented NTRK gene fusion.,
Phase 2: Infants from birth and older at C1D1 with a locally advanced or metastatic infantile fibrosarcoma, Patients with locally advanced infantile fibrosarcoma who would require, in the opinion of the Investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection, with documented ETV6 rearrangement (or NTRK3 rearrangement after discussion with the Sponsor) by FISH or RT-PCR or a documented NTRK fusion by e.g. NGS.
or:
Birth through 21 years of age at C1D1 with a locally advanced or metastatic solid tumor or primary CNS tumor that has relapsed, progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy with a documented NTRK gene fusion with the exception of patients with IFS (Infantile FibroSarcoma), CMN (Congenital Mesoblastic Nephroma tumors) or SBC (Secretory Breast Cancer), they may enroll into this cohort with documentation of an ETV6 rearrangement by FISH or RT-PCR. Documented NTRK fusion by NGS (Next Generation Sequencing) shall be identified through molecular assays as routinely performed at CLIA or other similarly-certified laboratories. If CLIA or similar certification of the laboratory performing the molecular assay is not confirmed at the time of consent patients may be included after discussion with the Sponsor. Patients with NTRK-fusion positive benign tumors are also eligible.
or:
(including Expansion Phase) Potential patients older than 21 years of age with a tumor diagnosis with histology typical of a pediatric patient and an NTRK fusion may be considered for enrollment following discussion between the local site Investigator and the Sponsor.,
2. Patients with primary CNS tumors or cerebral metastasis:
a) Must be neurologically stable based on stable neurologic exam for 7 days prior to enrollment.
b) Must have not required increasing doses of steroids within the 7 days prior to study entry to manage CNS symptoms
c) Phase 2 only: Imaging study must be performed within 28 days of C1D1 while

on stable dose steroid medication (if needed) for at least 7 days immediately before the imaging study., 3. Histologic verification of malignancy at original diagnosis or relapse, except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of cerebral spinal fluid (CSF) or serum tumor markers including alpha-fetoprotein or beta-human chorionic gonadotropin (HCG)., 4. Evaluable and/or measurable disease
a) Phase 1: Subjects must have evaluable and/or measurable disease as defined by RECIST, RANO or INRC.
b) Phase 2: Subjects with a solid or CNS tumor must have at least one measurable lesion as defined by RECIST, version 1.1, RANO or INRC. , 5. Karnofsky (those 16 years and older) or Lansky (those younger than 16 years) performance score of at least 50., 6. Patients must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy.
a) Myelosuppressive chemotherapy: At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea)
b) Investigational agent or anticancer therapy other than chemotherapy: Not within 2 weeks prior to planned start of larotrectinib or 5 half-lives, whichever is shorter. Full recovery of clinically significant toxicities from that therapy must be evident.
c) Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g., Neulasta) or 7 days for short-acting growth factor
d) Immunotherapy: At least 42 days after the completion of any type of immunotherapy (except for steroids), e.g., immune checkpoint inhibitors and tumor vaccines
e) X-ray therapy (XRT): At least 14 days after local palliative XRT (small port); >=At least 42 days must have elapsed if other substantial bone marrow (BM) radiation, including prior radio iodized metaiodobenzylguanidine (131I-MIBG) therapy.
f) Stem cell infusion without total body irradiation (TBI): No evidence of active graft versus host disease and at least 56 days must have elapsed after transplant or stem cell infusion., 7. An archival tumor tissue sample must be available. If archival tumor tissue sample is not available, a fresh biopsy (at a primary or at one metastatic site) should be performed. , 8. For patients without known bone marrow involvement:
a) Absolute neutrophil count (ANC) >=1.0 * 109/L and
b) Platelet count >=100.0 * 109/L (transfusion allowed)
c) Hemoglobin >=8.0 g/dL (transfusions allowed), 9. Patients with bone marrow involvement will not be evaluable for hematologic DLT and can enroll with:
a) ANC >=0.75 * 109/L and
b) Platelet count >=50.0 * 109/L (transfusions allowed)
c) Hemoglobin >=8.0 g/dL (transfusions allowed), 10. Adequate hepatic and renal function, defined as:
a) Bilirubin (sum of conjugated + unconjugated) <=2.5 * upper limit of normal (ULN) for age (patients with documented Gilbert*s Disease may be enrolled with Sponsor approval)

b) SGPT (ALT) <=2.5 * upper limit of normal.
c) Estimated glomerular filtration rate >=30 mL/min/1.73 m2 based on local institutional practice for determination, or a minimum serum creatinine as presented in Section 4.1,
11. Ability to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.,
12. Willingness of male and female patients with reproductive potential to use double effective birth control methods, defined as one used by the patient and another by his/her partner, for the duration of treatment and for 1 month following study completion., For male patients with a non-pregnant female partner of child-bearing potential and woman of child bearing potential one of the following highly effective birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended:
a) Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
b) Progestogen-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant
c) Intrauterine device (IUD)
d) Intrauterine hormone-releasing system (IUS)
e) Bilateral tubal occlusion
f) Vasectomized partner
g) Sexual abstinence: considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.
Birth control methods unacceptable for this clinical trial are:
a) Periodic abstinence (calendar, symptothermal, or post-ovulation methods)
b) Withdrawal (coitus interruptus)
c) Spermacide only
d) Lactational amenorrhea method,
13. Ability to swallow capsules, liquid or gastric access via a naso- or gastric tube,
14. Parent/g

Exclusion criteria

Patients meeting any of the following criteria are to be excluded from study participation:
1. Major surgery within 14 days (2 weeks) prior to C1D1., 2. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to C1D1; ongoing cardiomyopathy; or current prolonged QT interval corrected for heart rate (QTc) interval >480 milliseconds., 3. Active uncontrolled systemic bacterial, viral, or fungal infection., 4. Malabsorption

syndrome or other condition affecting oral absorption., 5. Current treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor or inducer other than those allowed per Section 6.3.2., 6. Pregnancy or lactation., 7. Phase 2 only: Prior progression while receiving approved or investigational tyrosine kinase inhibitors targeting TRK, including entrectinib, crizotinib and lestaurtanib. Patients who received a tropomyosin-related kinase (TRK) inhibitor for less than 28 days of treatment and discontinued because of intolerance remain eligible.

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):	04-07-2019
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Larotrectinib

Ethics review

Approved WMO

Date:	23-01-2018

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-09-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-05-2022
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2022-502668-20-00
EudraCT	EUCTR2016-003498-16-NL
ClinicalTrials.gov	NCT02637687
CCMO	NL63143.078.17