A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients with Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1)

Published: 11-09-2019
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This study has been transitioned to CTIS with ID 2024-512606-25-00 check the CTIS register for the current data. Primary Objective phase 2 part of the study- To determine the confirmed Objective Response Rate (ORR) as assessed by Blinded Independent...

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

Summary

ID

NL-OMON54586

Source
ToetsingOnline

Brief title
TRIDENT-1

Condition

- Other condition

Synonym
Advanced solid tumors. Cancer

Health condition

Advanced solid Tumors harboring ALK, ROS1 or NTRK1-3 rearrangements

Research involving

Human

Sponsors and support

Primary sponsor: Turning Point Therapeutics (a wholly owned subsidiary of Bristol Myers Squibb company)
Source(s) of monetary or material Support: Turning Point Therapeutics.(a wholly owned subsidiary of Bristol Myers Squibb company)

Intervention

Keyword: Advanced solid tumors

Outcome measures

Primary outcome

Primary Endpoint for Phase 2:

• Objective Response Rate (ORR) assessed by BICR using RECIST v1.1.

Secondary outcome

Secondary Endpoints for Phase 2:

• Duration of Response (DOR), Time to Response (TTR), and Clinical Benefit Rate

(CBR)

• Intracranial tumor response in subjects with measurable brain metastases, as

determined by BICR using modified RECIST v1.1

• CNS Progression-Free Survival (CNS-PFS) in subjects with measurable brain

metastases using modified RECIST v1.1

• Progression-Free Survival (PFS), and OS

Study description

Background summary

This study is testing a drug called repotrectinib and is being studied as a possible treatment for advanced or solid tumours in patients that are known to have rearrangement (mutation) in the ALK, ROS or NTRK 1-3 genes.

The proposed study comprises phase 1 and phase 2 portions as indicated in the title of the protocol. Enrollment in Phase 1 is completed and the recommended Phase 2 Dose (RP2D) of repotrectinib was established as 160 mg once daily for the first 14 days and may be increased to 160 mg twice daily. Repotrectinib can be taken with or without food. The EU (including the Netherlands) will take part in only Phase 2 of the study.

The phase 2 portion of study is to determine whether repotrectinib is effective cancer treatment, especially in groups of participants whose tumours have the gene mutations mentioned above. The study will also continue to look at the side effects and response of tumours to different doses, as well as how different foods affect how repotrectinib gets into the body. The study will include approximately 630 participants between 6 treatment groups based on the participant's tumour's gene mutation and previous cancer treatment:
Group 1. Participants that have the ROS1 gene mutation and have not undergone any previous tyrosine kinase inhibitor (TKI) therapy i.e. TKI-naïve, and a diagnosis of non small cell lung cancer (NSCLC).
Group 2. Participants that have had one round of TKI therapy and 1 platinum-based chemotherapy, with the ROS1 gene mutation and a diagnosis of NSCLC.
Group 3. Participants that have had two rounds of TKI therapy and NO chemotherapy or immunotherapy, with the ROS1 gene mutation and a diagnosis of NSCLC.
Group 4. Participants with the ROS1 gene mutation with a diagnosis of NSCLC advanced solid tumours and have previously received 1 ROS1 TKI therapy and NO chemotherapy or immunotherapy.
Group 5. Participants with the NTRK genes mutation with a diagnosis of advanced solid tumours, that have not previously received TRK treatment with TKI therapy.

Group 6. Participants with the NTRK genes mutation with a diagnosis of advanced solid tumours, that have previously received TKI therapy, chemotherapy and immunotherapy treatment.
All patients will take repotrectinib as a capsule taken by mouth at the RP2D

(160 mg once daily for the first 14 days and
which may increase to 160 mg twice daily depending on tolerability).
Phase 2 of this study consists of a Screening Phase and multiple Study Cycles (each cycle is about 28 days).
Participants will need to visit the study site to complete study procedures as follows:
• Screening Phase to determine if participants are eligible for the study (within 28 days of the first dose of
repotrectinib).
- Several visits may be required to perform the screening assessments.
• Study Cycles
- Cycle 1: Day 1, Day 8, Day 15, and Day 22
- Cycle 2: Day 1 and Day 15
- Cycle 3 (and then every 4 weeks): Day 1
• End-of-Treatment visit (within 7 days after the last dose of repotrectinib and after the decision to end treatment).
• Safety Follow-up visit (28 days after the last dose of repotrectinib)

Study objective

This study has been transitioned to CTIS with ID 2024-512606-25-00 check the CTIS register for the current data.

Primary Objective phase 2 part of the study
- To determine the confirmed Objective Response Rate (ORR) as assessed by Blinded Independent Central Review (BICR) of repotrectinib in each subject population expansion cohort of advanced solid tumors that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.

Secondary Objectives phase 2 part of the study
- To determine the Duration of Response (DOR), time to response (TTR), and clinical benefit rate (CBR) of repotrectinib, as assessed by BICR, in each subject population expansion cohort of advanced solid tumors that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.

- To estimate the progression-free survival (PFS) and overall survival (OS) of subjects treated with repotrectinib with advanced solid tumors that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.

- To evaluate the safety and tolerability of repotrectinib when administered at the RP2D in subjects with advanced solid tumors that harbor a ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangement.

- To determine the intracranial objective response rate (IC-ORR) of repotrectinib and Central Nervous System PFS (CNS-PFS) in subjects presenting with measurable brain metastases at baseline, using modified RECIST v1.1

assessment.

-To confirm PK of repotrectinib at the RP2D.

- To assess treatment-related symptoms and general health status using validated instruments of subject-reported outcomes (EORTC-QLQ-C30 and LC-13 when applicable) in subjects treated with repotrectinib.

Study design

The Phase 2 portion of the study will be with single-agent repotrectinib at the identified RP2D and will enroll subjects with ROS1+, NTRK1+, NTRK2+, or NTRK3+ advanced solid malignancies.
The Phase 2 segment of this study will consist of 6 subject expansion cohorts (EXP) (described in the Inclusion Criteria).

Subjects in Phase 2 will receive 160 mg repotrectinib orally once daily for the first 14 days. This may be increased to 160 mg twice daily after the subject*s treating physician has evaluated the subject*s tolerability for repotrectinib on C1D15.

On Study Assessments (Phase 1 and Phase 2)
Tumor assessments will be performed at Screening, at the end of Cycle 2 (within the Phase 1a study this was approximately 7 weeks from the initial repotrectinib treatment ± 2 days; and in Phase 1c given the duration of Cycle 1 is 4 weeks, it will correspond to 8 weeks from the initial repotrectinib treatment ± 7 days), every 2 cycles (± 7 days) up to the end of Cycle 18 and then every 3 cycles (± 7 days) up to the end of Cycle 36 and then every 4 cycles (± 7 days) thereafter until documented progression of disease regardless of treatment delays resulting from toxicity, and at the End of Treatment (EOT) if more than 4 weeks have passed since the last imaging assessment). At EOT visit, the subject must undergo an EOT tumor assessment evaluation (CT or MRI; MRI of the Brain and Bone Scan, if applicable) PRIOR to treatment discontinuation to evaluate for radiologic disease progression if treatment is being discontinued for a reason other than BICR-confirmed radiographic disease progression. After treatment discontinuation, tumor assessments should continue at the current scan interval at the time of treatment discontinuation until a subject begins a new course of cancer therapy or withdraws consent if there is no BICR -confirmed radiologic progression at the time of treatment discontinuation.
An EOT Visit will be conducted within 28 days of last dose of repotrectinib.
Additionally, each subject will be contacted by telephone approximately every 3 months following study discontinuation until death, loss to follow-up, or withdrawal of consent in order to assess disease progression and survival status.
For Phase 2, all efforts should be made to obtain the EOT radiographic scan before treatment discontinuation, and where possible inform and discuss with

the Sponsor*s Medical Monitor when considering treatment discontinuation. Disease progression must be determined by BICR. For subjects in Phase 2 with CNS disease who have been on study for at least 2 cycles of treatment with a best response of Stable Disease (SD) per RECIST v1.1 AND without treatment-related grade >= 2 AEs, dose escalation to 160 mg BID will be allowed as per Investigator*s discretion and after discussion with the Sponsor*s Medical Monitor.
Subjects may continue repotrectinib treatment after clinical or radiographic progression if he or she is continuing to experience clinical benefit, in the opinion of the Investigator, and after discussion with the Sponsor Medical Monitor.
Safety will be monitored via laboratory assessments, physical examinations, electrocardiograms (ECG), vital signs, and AEs. Study assessments for the Phase 1 and Phase 2 portion will be performed as per the Study Calendars. In Phase 2, a Data Monitoring Committee (DMC) will be established to monitor safety and conduct benefit-risk assessment on a routine basis that will be outlined in a separate DMC charter.

Intervention

The Phase 2 portion of the study will be with single agent repotrectinib at the identified RP2D and will enroll subjects with ROS1+, NTRK1+, NTRK2+, or NTRK3+ advanced solid malignancies. Based on safety, PK and preliminary efficacy data obtained in Phase 1, the RP2D of repotrectinib 160 mg QD for the first 14 days, which may be increased to 160 mg BID after subject evaluation at C1D15.

Study burden and risks

Interviews Every visit
Physical examination Every visit
Vitals signs Every visit
Tumor biopsy Screening (if required) and about 1 week after starting treatment (optional)
Blood draws Every visit
Urine collection Every visit (except Cycle 2 Day 15)
Heart tests Screening, Cycle 1 Days 1 and 15, then once every month (less frequent after 4 months), and end of treatment
Tumor imaging tests Screening, and then every 2 months (less frequent after 18 months)
Cerebrospinal fluid sampling (optional) Only if your doctor does this as part of your regular treatment
Pregnancy tests Screening, and then every month

Very common treatment-related effects reported in 10% or more patients include the following:

• Dizziness, which can cause the feeling of being lightheaded, woozy, or unbalanced,
at times when standing up quickly. Less commonly, this may be associated with a drop in blood pressure or vertigo. Most of the symptoms were mild or moderate and did not affect activities of daily living such as preparing meals, bathing, shopping for groceries or clothes, or using the telephone. A few patients, have experienced serious or severe symptoms, described as unsteadiness while standing or walking and being unable to move. Dizziness was managed by dose interruptions or a dose reduction. Avoid driving or using heavy machinery if you are having symptoms of dizziness
• Dysgeusia, which is a distortion of the sense of taste, or a condition in which a foul, salty, rancid, or metallic taste sensation persists in the mouth. Less commonly, dry mouth or difficulty swallowing may occur.
• Paresthesia is a burning or prickling sensation that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body. Less commonly, paresthesia may occur in the mouth, in addition to numbness in the mouth, or a feeling of burning on top of your mouth and/or tongue.
• Gastrointestinal effects, that may include constipation, nausea, and less commonly, vomiting, diarrhea, reflux (liquid content of the stomach moves up into the throat), inflammation of the mouth or digestive tract lining, abdominal pain, an upset stomach or decreased appetite.
• Anemia caused by a decrease in red blood cells that carry oxygen, which can cause tiredness (fatigue) or may make you more susceptible to infections. A few patients have experienced severe anemia that required a blood transfusion.
• Ataxia is a sign of poor muscle control that may cause clumsy, voluntary movements. Less commonly, it may be associated with tremors, walking difficulty and balance, which may lead to a fall.
• Liver function laboratory tests showing liver enzyme increases (ALT, AST), and other less common liver test results such as GGT increase may occur. Your doctor will do blood tests to check your liver function during treatment.
• Creatine kinase, a laboratory test, may show an increase in the blood, which may be severe when certain tissues like muscles are damaged. Less commonly, blood lactate dehydrogenase may also be increased. Tell your doctor if you are feeling any new or worsening signs and symptoms of muscle problems such as unexplained muscle pain, tenderness, muscular weakness that may be severe or serious, or muscle spasms.

A complete list of all possible risks and side effects can be found in Appendix D of the applicable consent forms.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Histologically or cytologically confirmed diagnosis of locally advanced, or metastatic solid tumor (including primary CNS tumors) that harbors a ROS1 or NTRK1-3 gene fusion.

- Subject must have a documented ROS1 or NTRK1-3 gene fusion determined by either a) an approved medical device OR b) a non-approved medical device (for details please see the protocol).

- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.

- Age >= 12 (or age >=20 as required by local regulation)
Sponsor confirms that only persons 18 years of age and older will be enrolled in the Netherlands

- At least 1 measurable target lesion according to RECIST (v1.1) prospectively confirmed by Blinded Independent Central Radiology Review (BICR), selected by

the Sponsor, PRIOR to enrollment. Subjects with CNS-only measurable target lesion >= 10 mm as defined by RECIST (v1.1) are eligible.

Exclusion criteria

1. Concurrent participation in another therapeutic clinical trial. 2. Symptomatic brain metastases or leptomeningeal involvement. 3. History of previous cancer requiring therapy within the previous 2 years, except for squamous cell or basal-cell carcinoma of the skin, or any in situ carcinoma that has been completely resected. 4. Major surgery within 4 weeks of start of repotrectinib treatment. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (<=10 fractions) must have been completed at least 48 hours prior to study entry. 5. Clinically significant cardiovascular disease (either active or within 6 months prior to enrollment): myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (New York Heart Association Classification Class >= II), cerebrovascular accident or transient ischemic attack, symptomatic bradycardia, requirement for anti-arrhythmic medication. Ongoing cardiac dysrhythmias of CTCAE grade >=2. 6. Any of the following cardiac criteria: · Mean resting corrected QT interval (ECG interval measured from the onset of the QRS complex to the end of the T wave) for heart rate (QTc) > 470 msec obtained from 3 ECGs, using the screening clinic ECG machine-derived QTc value · Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec) · Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or any concomitant medication known to prolong the QT interval 7. Known active infections requiring ongoing treatment (bacterial, fungal, viral including HIV positivity). 8. Gastrointestinal disease (e.g., Crohn*s disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact on drug absorption. 9. Peripheral neuropathy, paresthesia, dizziness, dysgeusia, muscle weakness, ataxia grade >=2. 10. History of extensive, disseminated, bilateral, or presence of CTCAE grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis. Subjects with history of prior radiation pneumonitis are not excluded. 11. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or that may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study, or could compromise protocol objectives in the opinion of the Investigator and/or Turning Point Therapeutics. 12. Current use or anticipated need for drugs that are known to

be strong CYP3A inhibitors or inducers as listed in Appendix 5. 13. Additional exclusion criteria for subjects participating in the midazolam DDI sub-study: in addition to the strong CYP3A inhibitors or inducers listed in Appendix 5, subjects should not be taking any moderate inhibitors or inducers of CYP3A (moderate CYP3A inhibitors e.g.: erythromycin, verapamil, atazanavir, fluconazole, darunavir, diltiazem, delavirdine, aprepitant, imatinib, tofisopam, ciprofloxacin, cimetidine; moderate CYP3A inducers e.g.:bosentan, efavirenz, etravirine, modafinil) within 2 weeks of the lead-in midazolam dosing and until the DDI assessment portion is completed on Cycle 1 Day 15. Please refer to midazolam product package insert for complete information.

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):	20-03-2020
Enrollment:	23
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Repotrectinib
Generic name:	Repotrectinib

Ethics review

Approved WMO Date:	11-09-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-12-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2021

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-12-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-08-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	CTIS2024-512606-25-00
EudraCT	EUCTR2016-003616-13-NL
ClinicalTrials.gov	NCT03093116
CCMO	NL70981.042.19