A first-in-human (FIH) study of IDRX-42 in participants with metastatic and/or unresectable gastrointestinal stromal tumors (GIST)

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This study has been transitioned to CTIS with ID 2024-514930-19-00 check the CTIS register for the current data. This study aims to evaluate IDRX-42 administered to participants with metastatic and/or surgically unresectable GIST.

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

Summary

ID

NL-OMON53904

Source
ToetsingOnline

Brief title
StrateGIST 1

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
cancer, gastrointestinal stromal tumors

Research involving
Human

Sponsors and support

Primary sponsor: IDRX, Inc.

Source(s) of monetary or material Support: Industry

Intervention

Keyword: GIST, IDRX, IDRX-42, StrateGIST

Outcome measures

Primary outcome

Phase 1b (Exploratory Cohorts)

Primary:

Safety:

• Further characterize the safety and tolerability of IDRX-42 in participants

with metastatic and/or surgically unresectable GIST

Efficacy:

• Evaluate the antitumor activity of IDRX-42 in participants with metastatic

and/or surgically unresectable GIST

Secondary outcome

Secondary:

• Further evaluate preliminary antitumor activity of IDRX-42 in participants

with metastatic and/or surgically unresectable GIST

• Characterize the PK profile of IDRX-42 in participants with metastatic and/or

surgically unresectable GIST

Study description

Background summary

Similar results were seen in a xenograft model expressing secondary resistance mutations in KIT exon 17.

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There is a high unmet medical need for effective treatments for patients with imatinib- and other tyrosine kinase inhibitor-resistant GIST driven by mutational variants that are not controlled by available therapies. IDRX-42 is highly active against KIT mutations in exons 11, 13, and 17, with high kinase selectivity, and excellent metabolic stability, permeability, and solubility.
IDRX-42 (formerly M4205, substance code MSC2700000A) is a potent, highly selective, orally administered, small molecule tyrosine kinase inhibitor, targeting disease-specific oncogenic drivers and a range of clinically relevant resistance mutations of KIT. IDRX-42 is being evaluated as a treatment for patients with metastatic and/or surgically unresectable GIST. In preclinical studies of IDRX-42 in GIST xenograft models expressing mutations in exon 11, IDRX-42 demonstrated superior antitumor activity compared with imatinib. In xenograft models expressing secondary resistance mutations in KIT exon 13, IDRX-42 treatment resulted in strong and dose-dependent antitumor activity, comparable to the second-line standard of care agent, sunitinib.
Similar results were seen in a xenograft model expressing secondary resistance mutations in KIT exon 17.

Study objective

This study has been transitioned to CTIS with ID 2024-514930-19-00 check the CTIS register for the current data.

This study aims to evaluate IDRX-42 administered to participants with metastatic and/or surgically unresectable GIST.

Study design

This is a FIH, Phase 1/1b, open-label study in participants with metastatic and/or surgically unresectable GIST. The study of IDRX-42 will occur in participants after failure of at least prior imatinib in dose escalation and confirmation (Phase 1) and cohorts 1, 2 and 4 (Phase 1b). Participants who are treatment naïve (first line therapy) and refused or are ineligible for other standard of care (SOC) therapies will be treated under Cohort 3 (Phase 1b). Inter-dose level dose escalation per modified Fibonacci design will be performed to assess DLTs and determine the MTD and/or RP1bD(s). Cohorts that explore participants with various prior lines of therapy at the RP1bD(s) will be added in Phase 1b to assess the preliminary antitumor effect of IDRX-42 and further characterize the safety profile.

Phase 1 Dose Escalation
IDRX-42 dose level escalation will use a standard 3 + 3 design. The starting dose (dose level [DL]1) will be 120 mg QD of IDRX-42 capsules. Up to 6 participants will be enrolled at DL1. More than 3 participants may be enrolled to ensure that at least 3 DLT-evaluable participants are available for

analysis. If none of the first 3 evaluable participants experience a DLT during the first cycle (28 days), up to 6 participants may be enrolled into the next DL.
If 1 DLT is observed at any DL, up to 3 more participants (for a total of 6 per DL) will be treated at the same DL. If no additional DLTs are observed, participants may be enrolled into the next DL. If 2 or more DLTs are observed at any DL, then the MTD will be defined as the previous DL examined. See protocol Section 6.1.1 for proposed dose escalation DLs for IDRX-42. Additional DLs and cohorts may be added depending on emerging safety data. During the dose escalation portion of the study, selected DLs may be backfilled with additional participants to acquire additional safety, pharmacodynamic, and response data once the safety review committee (SRC) has determined the dose is safe. Any backfill of selected cohorts requires approval from the Medical Monitor and no more than a total of 12 participants will be enrolled in any cohort. Based on the evaluation of the clinical data and PK profiles of IDRX-42, alternate schedules may be explored, including twice daily (BID) dosing.
Further description of the DLT evaluation period including DLT definitions is found in Section 6.1.1.2.
In the absence of an MTD, a maximum planned dose will be declared. This study will utilize a SRC, tasked with reviewing all available safety information. The SRC is responsible for dose escalation decisions including whether a waiting period for any or all participants enrolled into a new cohort will be required, if additional participants should be enrolled at a particular dose level (resulting in > 6 participants), or if intermediate or additional dose levels should be evaluated. The SRC will be composed of Principal Investigators, Sponsor, and contract research organization medical representatives.

Phase 1 Dose Confirmation
Additional participants (up to approximately 30 total) may be added to selected DLs to acquire additional safety, pharmacodynamic, and response data.
The selection of the DL(s) for further study will be guided by available participants* safety, PK, pharmacodynamic, and antitumor activity data.
The RP1bD(s) will be chosen based on a holistic review of Phase 1 participants* safety, antitumor activity, PK, and pharmacodynamic data by the SRC.

Phase 1b Exploratory Cohorts
Upon determination of RP1bD(s) in the Phase 1 portion of the study, Phase 1b may commence to evaluate the RP1bD(s) of IDRX-42 in participants with GIST. Phase 1b of the study is planned to further evaluate preliminary antitumor activity, safety, and tolerability of IDRX-42, and characterize the PK and pharmacodynamic profile of IDRX-42 in participants with metastatic and/or unresectable GIST. Enrollment into 4 exploratory cohorts can occur simultaneously for each of the following participant populations. If two doses are explored in Phase 1b, a 1:1 randomization may be utilized for assignment of dose within each cohort:
Cohort 1: Metastatic and/or surgically unresectable GIST participants who have progressed on imatinib only (second line therapy) and refused or are ineligible

for other standard of care (SOC) therapies
Cohort 2: Metastatic and/or surgically unresectable GIST participants who have progressed on both imatinib and sunitinib (third line therapy) or progressed on imatinib, sunitinib, and an additional agent (i.e., regorafenib or ripretinib) (fourth line therapy), or progressed on imatinib, sunitinib, regorafenib, and ripretinib (fifth line or greater therapy)
Cohort 3 Applicable in US, UK, China, and South Korea Only: Metastatic and/or surgically unresectable GIST participants who are treatment naïve (first line therapy) and refused or are ineligible for other standard of care (SOC) therapies
Cohort 4: Participants who meet the same criteria as Cohort 2 (third line or greater) and have also had prior treatment with investigational agents NB003 or THE-630 or a line of therapy of bezuclastinib plus sunitinib combination
IDRX-42 will be administered until disease progression, unacceptable toxicity, death, withdrawal of consent by participant, Investigator decision to discontinue treatment, Sponsor's decision to terminate the study, or other protocol specified reason for discontinuation of study treatment.

Recommended Dose Modification Guidelines
Dose modification guidelines for IDRX-42-related toxicity are summarized in Table 6 in the protocol. Deviation from these guidelines must be discussed with the study Medical Monitor.

Response Assessments
The primary efficacy assessment endpoint in Phase 1 is ORR as determined by Investigator response assessments per mRECIST v1.1 response criteria (Demetri 2013) based upon imaging scans performed at the time points outlined in the Schedule of Assessments (Table 1). Additional Phase 1 efficacy assessment endpoints include PFS, TTR, and DOR. The primary efficacy endpoint in Phase 1b is ORR as determined by Independent Review response assessments per mRECIST v1.1 criteria (Demetri 2013) based upon imaging scans performed at the time points outlined in the Schedule of Assessments (Table 1). Additional Phase 1b efficacy assessment endpoints include PFS, CBR, TTR, and DOR.
Response assessments will be conducted at C2D1, C3D1, C5D1, and every 2 cycles thereafter.

Safety Assessments
Safety will be assessed by adverse events (AEs), physical examinations, vital signs, hematology and chemistry laboratories, and electrocardiograms (ECGs). AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the time of database creation and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) version 5.0 or higher. The MedDRA dictionary may be up-versioned once per year.

Pharmacokinetic/Pharmacodynamic Assessments
Blood samples will be taken pre-dose and at various time points throughout the

study in order to characterize the PK of IDRX-42 in participants with metastatic and/or surgically unresectable GIST (Table 2). In order to determine the effects of IDRX-42 on mutational burden as a measure of pharmacodynamic activity in participants with metastatic and/or surgically unresectable GIST, blood will be obtained at various time points throughout the study (Table 2).

Intervention

IDRX-42 will be administered orally daily in continuous 28-day cycles in both Phase 1 and Phase 1b of this study.

Study burden and risks

The primary therapy for patients with resectable or potentially resectable GIST is surgery. However, recurrence occurs in more than half of patients with resectable disease. For most patients with metastatic and/or surgically unresectable GIST, first-line treatment with imatinib demonstrates limited effectiveness. Frequently secondary mutations lead to drug resistance, necessitating treatment with second-, third-, and fourth line therapies such as sunitinib, regorafenib, and ripretinib, respectively. Heterogeneous activating mutations that are resistant to existing kinase inhibitors limit the clinical benefit of these therapies. Thus, there remains a high unmet need for an effective treatment for metastatic or unresectable GIST.
Based on the results of the toxicology studies, IDRX-42 comprises a nonclinical safety profile that is adequate for the treatment of patients suffering from life-threatening malignancies. Repeat-dose toxicity studies showed that the main target organs of toxicity are the hematopoietic system, male reproductive organs, and the liver. These are known effects for the drug class of KIT inhibitors and have been observed with currently available KIT inhibitors. No indications for phototoxicity of IDRX-42 were observed, and the genotoxic risk of IDRX-42 is considered to be low. Metabolism is the predominant elimination pathway prior to excretion and importantly, no human-specific metabolites were identified following cross-species in vitro metabolism assessments in hepatocytes.
Recommendations during clinical use include the monitoring of main target organs of toxicity determined in general toxicity testing including standard hematological monitoring with complete blood counts and monitoring of hepatic enzymes. As no formal data are available on reproductive and developmental toxicity, a strict use of contraceptives for male participants under treatment and for women of childbearing potential is considered mandatory.
Overall, the nonclinical profile supports the evaluation of IDRX-42 in participants with metastatic and/or surgically unresectable GIST, a life-threatening condition with a high unmet need with the MRSD for the FIH study of 120 mg/day (Section 4.3.2).

Contacts

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Eligible participants are adults who have metastatic and/or surgically unresectable GIST. A full list of inclusion and exclusion criteria are found in Section 7.1 and Section 7.2.
Key Inclusion Criteria:
1. >=18 years of age
2. Histologically or cytologically confirmed metastatic and/or surgically unresectable GIST
3. Documented progression on imatinib (Phase 1)
4. Documented pathogenic mutation in KIT OR any PDGFRA mutation other than exon 18 mutations, determined through local testing
5. At least one measurable lesion by mRECIST v1.1 for participants with GIST (Demetri 2013)

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. Resolution of any toxicities from prior treatment(s) to <= Grade 1 by NCI CTCAE v5.0, or have resolved to baseline, at the time of first dose of study drug.
Note: unresolved prior treatment-related Grade 2 alopecia, Grade >=2 peripheral neuropathy, and Grade >=2 hypothyroidism on a stable dose of thyroid hormone replacement therapy are allowed if deemed irreversible.
8. Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures and study restrictions.

Additional Inclusion Criteria for Phase 1b Exploratory Cohorts:
1. For Cohort 1, progressed on imatinib only (second line therapy) and refused or are ineligible for other SOCs
2. For Cohort 2, progressed on both imatinib and sunitinib (third line therapy), or progressed on imatinib, sunitinib, and an additional agent (i.e., regorafenib or ripretinib) (fourth line therapy), or progressed on imatinib, sunitinib, regorafenib, and ripretinib (fifth line or greater therapy)
3. For Cohort 3 (applicable in US, UK, China, and South Korea only), treatment naïve (first line therapy) and refused or are ineligible for other standard of care (SOC) therapies
4. For Cohort 4, met the same criteria as Cohort 2 (third line or greater) and have also had prior treatment with investigational agents NB003 or THE-630 or a line of therapy of bezuclastinib plus sunitinib combination.

Exclusion criteria

Key Exclusion Criteria:
1. Any prior treatment with investigational agents NB003 or THE-630 or a line of therapy of bezuclastinib plus sunitinib combination (except for participants treated in Cohort 4 of Phase 1b).
2. GIST that is both KIT and PDGFRA wild-type.
3. Primary brain malignancy or known untreated or active central nervous system metastases.
4. Has an active uncontrolled infection, including, but not limited to, the requirement for intravenous antibiotics.
5. Has significant, uncontrolled, or active cardiovascular disease.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-05-2024
Enrollment:	3
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	IDRX-42
Generic name:	IDRX-42

Ethics review

Approved WMO Date:	18-01-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	09-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-02-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-02-2024
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	CTIS2024-514930-19-00
EudraCT	EUCTR2022-001192-14-NL
CCMO	NL82517.041.22
Other	www.clinicaltrialsregister.eu / clinicaltrials.gov