A Phase 2, Adaptive, Open-Label, Multiple-Dose, Dose-Escalation Study to Evaluate the Efficacy, Safety,Tolerability, and Pharmacokinetics of Intravenous AMB-05X in Subjects with Tenosynovial Giant Cell Tumor

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The objectives of this study are to evaluate the safety, efficacy, and pharmacokinetics (PK) of AMB-05X in the treatment of tenosynovial giant cell tumor (TGCT)

Ethical review	Approved WMO
Status	Pending
Health condition type	Synovial and bursal disorders
Study type	Interventional

Summary

ID

NL-OMON50912

Source
ToetsingOnline

Brief title
A Study to evaluate treatment with IV AMB-05X in subjects with TGCT

Condition

- Synovial and bursal disorders

Synonym
Giant cell tumor

Research involving
Human

Sponsors and support

Primary sponsor: AmMax Bio Inc
Source(s) of monetary or material Support: Industry

Intervention

Keyword: infusion, intra-venous, TGCT

Outcome measures

Primary outcome

Frequency and severity of reported treatment-emergent adverse events (TEAEs)

Secondary outcome

Efficacy:

The following efficacy endpoints will be assessed at Week 12:

• The proportion of subjects who achieve an overall tumor response (objective response [OR], which includes both complete response [CR] and partial response [PR]) per the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) at Week 12.

• Proportion of subjects with overall response based on tumor volume score (TVS), a TGCT-specific method that calculates tumor volume as a percentage of the estimated maximally distended synovial cavity

• Mean change from Baseline in range of motion (ROM) score

• Mean change from Baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function score

• Mean change from Baseline in Worst Stiffness Numeric Rating Scale (NRS) score

• Percentage of subjects who respond with a decrease of at least 30% in mean

Brief Pain Inventory (BPI) score from Baseline

• Mean change from Baseline in BPI score

• Mean change from Baseline in Worst Pain NRS score

• Mean change from Baseline in EQ-5D-5L health assessment

Pharmacokinetics and Pharmacodynamics:

• Serum (and optional synovial) AMB-05X levels

• Serum (and optional synovial) AMB-05X-binding anti-drug antibody (ADA) levels

• Serum (and optional synovial) colony-stimulating factor 1 (CSF1) levels

Study description

Background summary

AMB-05X drug substance is a human monoclonal antibody against the colony-stimulating factor 1 receptor (CSF1R). This drugcandidate is thought to block the growth-promoting activity in TGCT. Given the limitations of current treatment options, thelocalized nature of the disease and prior clinical validation of CSF1R as an effective treatment target, AMB-05X is being developedby the sponsor.

Study objective

The objectives of this study are to evaluate the safety, efficacy, and pharmacokinetics (PK) of AMB-05X in the treatment of tenosynovial giant cell tumor (TGCT)

Study design

This is a Phase 2, open-label, multiple-dose, dose-escalation study with an adaptive design that will enroll up to approximately 36 subjects with TGCTfor 12 weeks of open-label treatment with intravenous (IV) AMB-05X. Each subject will receive a dose of AMB-05X every 2 weeks, for a total of 6 doses over the 12-week treatment period.

The study will enroll up to 3 dose cohorts each composed of 3 to 12 subjects.

The following dose cohorts are planned:
-Cohort A: Initial dose of 4 mg/kg, followed by 5 doses of 2 mg/kg
-Cohort B: Initial dose of 8 mg/kg, followed by 5 doses of 4 mg/kg
-Cohort C: Initial dose of 12 mg/kg, followed by 5 doses of 8 mg/kg
Based on its ongoing data review, the Sponsor may elect to enroll cohorts in a staggered and/or overlapping manner (initiating enrollment in the next cohort while the previous cohort is still completing or still enrolling) or sequentially (waiting until more complete data are available from the current cohort before initiating the next cohort).

A study schema is provided in Section 1.2, and the Schedule of Events is provided in Section 1.3. There will be a screening period of up to 4 weeks, a treatment period of 12 weeks, and a post-treatment follow-up period of 12 weeks.

A Sponsor data monitoring committee (DMC) composed of qualified medical/clinical representatives will review the available safety, tolerability, PK, pharmacodynamics (PD), and efficacy data on an ongoing basis and provide recommendations regarding appropriate next steps in study conduct, including any change in planned doses. The DMC will begin to review study data after the first 3 subjects complete Week 6 and continue to review data throughout the study (each time at least 3 additional subjects [from any cohort] complete Week 12). Study enrollment and conduct may continue unchanged during DMC review.

If a change in dose is made during the study, the DMC will again review the available data once 3 subjects have completed Week 6 at the new dose and provide further recommendations.

The Investigator may exercise his/her clinical judgment and consider a reduction in an individual subject*s maintenance dose (from 2 mg/kg to 1 mg/kg, 4 mg/kg to 2 mg/kg, or 8 mg/kg to 4 mg/kg) for subjects who experience a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher adverse event (AE) considered at least possibly related to study drug (see Section 7.4.3). Before implementing a dose reduction for a subject, the Investigator should contact the Medical Monitor to discuss the case.

Intervention

The Schedule of Events is provided in Section 1.3 of the protocol

Study burden and risks

The patients will come to the hosptial 10 times, treatment will take place 6 times.

Risks associated with assessments done during these visits:

- Blood collection: Blood will be collected from a vein in the arm during this study. Approximately 70 ml taken at some study visits (See section J of the ABR form). Possible side effects or risks from blood collection include swelling of the vein, pain, bruising, or bleeding at the site of collection,feeling faint or dizzy.
- Optionally, approximately 2 ml of synovial fluid will be taken at 2 study visits. Possible side effects or risks from synovial fluid collection are bleeding, soreness or stiffness in the joint.
- ECG: Skin irritation could occur from the electrodes or gel that is used.
- Questionnaires/Tests of simple tasks: There are no physical risks associated with these questionnaires/tests.
- confidentiallity, however all is done to comply with GDPR.
- common side effects: Fatigue (feeling tired), facial swelling, increases in liver enzyme tests (changes in tests that measure thefunctioning of your liver), rash, itch, decrease appetite. Because the drug AMB-05X is investigational, there may be other risks thatare unknown.
- Sometimes, people have severe allergic reactions to drugs. A severe allergic reaction could be life-threatening and may result indeath. Symptoms of possible allergic reactions include rash, difficulty breathing, coughing, wheezing, sudden drop in bloodpressure, swelling of the mouth, throat or eyes, seizures, flushing, fainting, a fast pulse and sweating.

AMB-05X may lead to improvement of the disease, but this is not certain.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female >=18 years of age.
2. Able to communicate well with study staff, understand and comply with the requirements of the study, and read and voluntarily sign the informed consent form (ICF) before the conduct of any study-specific procedures. .
3. TGCT that meets both of the following criteria:
a. Diagnosis has been histologically confirmed by a pathologist. If the diagnosis has not been previously histologically confirmed, biopsy with histological confirmation is required before enrollment.
b. Has not been surgically resected either because surgical resection would be associated with potentially worsening functional limitation/ severe morbidity (locally advanced disease) or because the subject declined surgery.
4. Measurable disease as defined by RECIST v1.1 (except with a minimum size of 2 cm), assessed from MRI scans by a central radiologist.
5. Symptomatic disease defined as one or both of the following:
a. A score of at least 4 on the Worst Pain NRS at Screening.
b. A score of at least 4 on the Worst Stiffness NRS at Screening.
6. Stable prescription of analgesic regimen during the 2 weeks before Baseline.
7. Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline.
8. Agrees to follow contraception guidelines (see Section 5.3).
9. Adequate hematologic, hepatic, and renal function at Screening, defined by:
• Absolute neutrophil count >= 1.5 × 109/L
• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 1.5 × upper limit of normal (ULN)
• Hemoglobin > 10 g/dL
• Total bilirubin <= 1.5 × ULN
• Platelet count >= 100 × 109/L
• Serum creatinine <= 1.5 × ULN
10. Willing and able to complete the PROMIS Physical Function Scale, Worst Stiffness NRS, BPI, and EQ-5D-5L throughout the study.

Exclusion criteria

1. Use of any investigational drug within 4 weeks or 5 half-lives (whichever is longer) before baseline.
2. Any previous use of pexidartinib or any biologic treatment targeting CSF1 or CSF1R. Use of an oral tyrosine kinase inhibitor other than pexidartinib (eg, imatinib or nilotinib) within 3 months before Baseline.
3. Active cancer (either currently or within 1 year before Baseline) that requires/required therapy (eg, surgery, chemotherapy, or radiation therapy), with the exception of adequately treated basal or squamous cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix or breast, or prostate carcinoma not requiring treatment apart from active surveillance.
4. Known metastatic TGCT.
5. Hepatitis C virus (HCV) or hepatitis B virus (HBV) or known active or chronic infection with human immunodeficiency virus (HIV).
6. Known active tuberculosis (TB).
7. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history that, in the Investigator's opinion, would likely interfere with the subject*s study participation or the interpretation of the subject*s results.
8. A woman who is breastfeeding.
9. A screening Fridericia-corrected QT interval (QTcF) >=450 ms (men) or >=470 ms (women)
10. MRI contraindications (eg, pacemaker, loose metallic implants)
11. History of hypersensitivity to any ingredient in the study drug.
12. History of drug or alcohol abuse within 3 months before Baseline.
13. Has any other severe acute or chronic medical or psychiatric condition or clinically significant laboratory abnormality that may increase the risk associated with study participation/treatment, interfere with interpretation of study results, or, in the Investigator*s opinion, make the subject inappropriate for this study.
14. A subject who, in the opinion of the Investigator, should not participate in this study for any reason, including instances where the subject*s stability or ability to comply with study requirements is in question.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	16-06-2021
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	AMB-05X
Generic name:	AMB-05X

Ethics review

Approved WMO

Date:	11-05-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	09-07-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	02-09-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
EudraCT	EUCTR2020-004870-22-NL
CCMO	NL75992.058.21
Other	US IND 100835