A Phase III, Multicentre, Randomised, Double-Blind Study to Assess the Safety and Efficacy of Emactuzumab vs. Placebo in Subjects with Tenosynovial Giant Cell Tumour.

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Primary:To estimate the treatment effect of emactuzumab on objective response rate (ORR) by 6 months from initiation of therapy in the blinded phase compared to placeboSecondary:the effect of emactuzumab on clinical outcome assessments (COAs) for:o...

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

Summary

ID

NL-OMON51288

Source
ToetsingOnline

Brief title
TANGENT

Condition

- Other condition
- Synovial and bursal disorders

Synonym
Malignant giant cell tumor, tenosynovial giant cell tumor (TGCT)

Health condition

Tenosynovial Giant Cell Tumour, Cancer

Research involving
Human

Sponsors and support

Primary sponsor: SynOx therapeutics Ltd
Source(s) of monetary or material Support: SynOx Therapeutics Limited

Intervention

Keyword: Emactuzumab, TGCT

Outcome measures

Primary outcome

• Objective response rate by 6 months from initiation of therapy based on

independent, blinded central review

Secondary outcome

Key secondary endpoint:

• Change in Patient-Reported Outcomes Measurement Information System-Physical

Function (PROMISPF) TGCT from baseline to 6 months

Other secondary endpoints

• Change in PROMIS-PF TGCT from baseline over time

• Physician/Healthcare Professional (HCP)-Reported Joint Mobility Score by

goniometry from baseline over time

• Change in Worst Pain Numerical Rating Scale (NRS) from baseline over time

• Change in Short Form 12-Item Survey version 2 (SF-12 v2) from baseline over

time

• Change in Worst Stiffness NRS from baseline over time

• PGI of change and severity over time

• Change in EuroQoL 5-Dimension, 5-Level questionnaire (EQ-5D-5L) from baseline over time

• Duration of response (DoR) as measured by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 based on independent, blinded central review

• Disease control rate (DCR) as measured by RECIST v1.1 based on independent, blinded central review

• Time to progression as measured by RECIST v1.1 based on independent, blinded central review

• Change in Tumour volume score (TVS) from baseline over time

• Surgical intervention rate, defined as the number of subjects who undergo surgery during the study for TGCT

Study description

Background summary

TGCTs are a group of generally benign intra-articular and soft tissue tumours with common histologic features, broadly divided into localised (lTGCT) and diffuse (dTGCT) types. The lTGCT include giant cell tumours of tendon sheath and pigmented villonodular synovitis and are generally indolent. dTGCT encompass conventional pigmented villonodular synovitis and diffuse-type giant cell tumour and are locally aggressive, invading extra-articular tissue with high risk for recurrence post surgery in at least 50% of cases. Most TGCTs are located in the knee, hip, ankle, wrist, and foot and are often severe and seriously debilitating. TGCT often leads to severe morbidity with accompanying pain and inability for patients to undertake daily activities. Surgery is often restricted due to the location and characteristics of the tumour. Further, surgery is often associated with long recovery times, poor outcomes and high recurrence rates, depending on the nature of the lesion. The disease often affects young adults who would otherwise be healthy and active, and can have a significant impact on education, work and family life (Mastboom et al, 2018a).

All TGCTs are clonal neoplastic tumours driven by overexpression of macrophage colony stimulating factor-1 (CSF-1). CSF-1 is a secreted cytokine/haematopoietic growth factor that plays an essential role in the proliferation, differentiation, and survival of monocytes, macrophages, and related cells. It is localised to the 1p13 breakpoint and appears to have a major oncogenic role in TGCT.

The M2-like subtype of tumour associated macrophages (TAMs) is implicated in promoting tumourigenesis and suppressing tumour immunity. Tumours are able to recruit and polarise macrophages into the M2-like subtype by secreting various cytokines such as CSF-1 and interleukin 10 (IL-10). CSF-1 is linked to neoplasia and poor prognosis. The CSF-1R tyrosine kinase, responsible for mediating the cellular effects of CSF-1, is therefore an attractive target to selectively inhibit TAMs of the M2-like subtype.

Emactuzumab is an investigational humanised mAb which binds specifically to human CSF-1R. Emactuzumab is not approved in any regulatory territory. Non-clinical data support its potential utility in TGCT reduction via CSF-1R inhibition. Emactuzumab shows non-linear pharmacokinetics (PK) and target-mediated drug disposition. After iv administration of emactuzumab at dose-levels >= 900 mg and different dosing intervals in man target saturation in excess of 90% was achieved over the entire dosing cycle, therefore leading to the selection of the 1000 mg dose every two weeks (Q2W).

Emactuzumab demonstrated pre-liminary clinical activity in a Phase Ia/b study (BP27772) involving 216 subjects with various underlying tumours. Of these, 63 subjects with TGCT received emactuzumab monotherapy, which included 51 subjects who received a dose of 1000 mg emactuzumab. The number of subjects with TGCT with a best unconfirmed complete response (CR) or partial response (PR; by central assessment) in the 1000 mg dose cohort was 35 of 51 subjects (68.6%). The Clinical Benefit Rate (CBR), ie, number of subjects with confirmed CR, PR, or stable disease (SD) by central assessment in the total cohort of subjects with TGCT was 96.8% (61 of 63 subjects). The confirmed CBR in the 1000 mg dose cohort (n = 51) was 98.0%.

Study objective

Primary:
To estimate the treatment effect of emactuzumab on objective response rate (ORR) by 6 months from initiation of therapy in the blinded phase compared to placebo

Secondary:
the effect of emactuzumab on clinical outcome assessments (COAs) for:
o Physical functioning
o Range of motion (ROM)
o Pain

o Stiffness
o Patient Global Impressions (PGIs)
o QoL

Further antitumour activity of emactuzumab in TGCT compared to placebo

Surgical Intervention Rate

Study design

SNX-301-202 is a Phase III, Multicentre, Randomised, Double-Blind Study to Assess the Safety and Efficacy of
Emactuzumab vs. Placebo in Subjects with Tenosynovial Giant Cell Tumour. in adult and adolescent subjects aged >=12 years. At study start subjects will be randomized in a 2:1 ratio to receive an intravenous (iv) infusion of either emactuzumab or placebo to one of the following treatment groups:

Group 1: 1000 mg emactuzumab administered as biweekly iv infusion over 90 minutes beginning on D1 for up to 5 cycles.

Group 2: placebo administered as biweekly iv infusion over 90 minutes beginning on D1 for up to 5 cycles.

Each adolescent subject (12 -17 years) will receive biweekly iv infusions of emactuzumab beginning on D 1 for up to 5 cycles (no randomization).
Group 3: 1000 mg emactuzumab administered as biweekly iv infusion over 90 minutes.

The approximate total duration of study participation for each subject is 2 years comprising the following periods:
• Screening: within 14 days prior to randomisation (Screening Visit).
• Double-Blind Treatment Period: 3 months from D 1 (Visit 1) to D 91 (Visit 7/End of Treatment/Early Discontinuation Visit).
• Double-Blind Follow-up Period: 21 months beginning after D 91 (Visit 7) to D 721 (Visit 14/End of Study Visit).

Crossover of Subjects Randomised to Placebo to Open-Label Treatment with Emactuzumab
If the adult subject is randomised to placebo, they will be eligible for treatment with emactuzumab in the Open-Label Phase under the following conditions:
• have completed at least the 6-month visit D 181 (Visit 10; 3 months treatment and 3 months observation) of the Double-Blind Phase
• have i) progressed according to RECIST v1.1 (objective progressive disease on MRI imaging centrally confirmed) within 6-18 months of initial treatment on D 1 (Visit 1), or ii) have stable disease according to RECIST v1.1 (on MRI imaging centrally confirmed) and clinically relevant deterioration as assessed by the

Investigator and confirmed by the Medical Monitor within 6-18 months of initial treatment on D 1 (Visit 1)
• are determined to have received placebo upon unblinding. Note: unblinding should only take place after all D 181 (Visit 10) assessments, including subject interviews, have been performed.

Retreatment of Subjects Receiving Emactuzumab as Initial Treatment
Adult and adolescent subjects who respond based on RECIST v1.1 to initial treatment with emactuzumab and then progress (objective progressive disease on MRI imaging centrally confirmed) within 9-18 months of initial treatment on D 1 (Visit 1), will be eligible for retreatment in the Open-Label Phase of the study. Retreatment will be at the discretion of the local Investigator following agreement with the Sponsor. A minimum 6-month washout period is included between treatments.

For subjects that are eligible for crossover treatment or retreatment with emactuzumab, the study will include the following additional periods:
• Open-Label Treatment Period: 3 months from D 1 - open-label (ol) (Visit 1-ol) to D 91-ol (Visit 7-ol/End of Treatment/Early Discontinuation Visit).
• Open-Label Follow-up Period: up to 2 years after randomisation in the Double-Blind Phase (ie, depending on time of subject entry into the Open-Label Phase, subjects may have a longer or shorter Open-Label Follow-up Period).

Intervention

The current study evaluates intravenously administered doses of emactuzumab. Each treatment dose is 1000mg, administered as IV infusion over 90 minutes, repeated Q2W for a maximum of 10 weeks (5 cycles).

Placebo will be presented as a sterile, colourless concentrate of excipients only, buffered at pH 6.0, in a single-use 10 mL vial. The placebo will be administered as iv infusion over 90 minutes, repeated Q2W for a maximum of 10 weeks (5 cycles).

Study burden and risks

Patients participating will receive 5 cycles of treatment on a biweekly basis over a period of 10 weeks. After end of treatment the patient will visit the clinic on a monthly basis for 3 months and on a 6 monthly basis for a year. Total duration will be 2 years.
the following will be assessed these visits: MRIs (6 in total), ECGs (5 in total), physical examinations, questionnaires on health and quality of life (each visit) and blood sampling at each visit (15-30mL at each visit), and assessment of any side effect at every visit.

A Data safety monitoring board is installed that will review study safety

listings on a regular basis. Responsibilities are:
1. To be responsible for safeguarding the interests of trial subjects and to assess in an unblinded way the safety of the IMPs.
2. To monitor evidence for treatment harm vs benefit, ie, toxicity, SAEs, deaths.
3. To confirm the acceptability of study continuation.
4. To advise on and/or review any major protocol modifications suggested by the Investigator or the Sponsor.
5. After the end of the trial, to read and comment on the Clinical Study Report.
At the end of each safety review meeting, the DSMB will issue a blinded report to the Sponsor, which should confirm whether study treatment should continue at the current dose, or if any Urgent Safety Measures/ protocol amendments are required.

Contacts

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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)

Inclusion criteria

1. Written informed consent.
2. 2. Biopsy-confirmed (standard of care diagnosis history) local or diffuse TGCT where surgical resection would be associated with predicted worsening functional limitations due to surgical damage to the joint and adjacent soft tissues, and/or subject presents with an anticipated high risk of early recurrence as determined by a multidisciplinary tumour board or equivalent*, or any other morbidity associated with the surgery, and/or surgical treatment is not expected to improve the clinical outcomes of the subject.
*The multidisciplinary tumour board or equivalent must comprise at least 2 individuals: the Investigator plus at least one other qualified physician (orthopaedic surgeon or medical oncologist) not involved in this study
3. Measurable disease: longest diameter >=20 mm.
4. Age >12 years.
5. Adequate organ and bone marrow function: haemoglobin (Hb) >10.0 g/dL, neutrophils >1.5 × 109/L and platelets >100 × 109/L.
6. Minimum mean score of 4 on NRS for Worst Pain during 7 days prior to randomization,
based upon a minimum of 4 days of completed diary data.
7. Minimum mean score of 4 on NRS for Worst Stiffness during 7 days prior to randomization, based upon a minimum of 4 days of completed diary data.
8. Women of childbearing potential (WOCBP) must have a negative urine and serum pregnancy test prior to starting treatment. WOCBP must agree to use a highly effective method of contraception throughout the treatment period and for 7 months after discontinuation of treatment. Acceptable methods of contraception according to protocol description.
9. For Open-Label Phase ONLY:
Subjects must either:
-Have responded based on RECIST v1.1 (CR or PR) to initial treatment with emactuzumab during the Double-Blind Phase and then progressed (objective progressive disease on imaging) within 9-18 months of initial treatment on D 1 (Visit 1) with a minimum 6-month washout period between treatments; or
-Have received placebo and completed the 6-month visit on D 181/Visit 10 (3 months treatment and 3 months observation) of the Double-Blind Phase and have not completed more than 18 months of the study since initial treatment on D1 (Visit1).

Exclusion criteria

1. Pregnant or breast feeding.
2. Medical conditions, including auto-immune, requiring systemic immunosuppression. Any

systemic treatment for these conditions (eg, glucocorticoids) is not allowed within
4 weeks of Screening and during the study. All Lupus Erythematosus are excluded irrespective of treatment.
3. Metastatic TGCT.
4. TGCT currently affecting multiple joints.
5. Pexidartinib therapy within 3 months of Screening.
6. Nilotinib, imatinib; other chemotherapy, radiotherapy, or investigational therapy within 4
weeks of Screening.
7. Unresolved clinically significant toxicity from a previous treatment or any history of
serious liver toxicity.
8. Current or chronic history of liver disease. This includes, but is not limited to, hepatitis
virus infections, drug- or alcohol-related liver disease, nonalcoholic steatohepatitis,
autoimmune hepatitis, haemochromatosis, Wilson*s disease, α-1 antitrypsin deficiency,
primary biliary cholangitis, primary sclerosing cholangitis, or any other liver disease
which in the opinion of the Investigator is considered clinically significant.
9. Renal function: creatinine clearance <60 mL/min (Cockcroft-Gault formula).
10. Liver function: ALT >3.0 × ULN; OR total bilirubin >1.5 × ULN.
11. Within 6 months of baseline has experienced: clinically significant myocardial infarction,
severe/unstable angina pectoris, congestive heart failure New York Heart Association
(NYHA) Class III or IV, or pulmonary disease (NYHA Criteria 1994).
12. Clinically significant active infection requiring systemic antibiotic treatment.
Rescreening may occur any time after 7 days post completion of treatment.
13. Systemic antiretroviral therapy within 3 months of baseline.
14. Other active cancer that requires concurrent treatment or history of malignancy other than
TGCT, unless there is the expectation that the malignancy has been cured, and tumor
specific treatment for the malignancy has not been administered within the previous
5 years.
15. Planned surgery during the course of the study with the exception of dental treatment.
16. Inability to comply with the study procedures.
17. For the Double-Blind Phase ONLY:
Previous exposure to emactuzumab and/or neutralizing antibodies.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	26-09-2022
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Emactuzumab
Generic name:	Emactuzumab

Ethics review

Approved WMO Date:	28-06-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-09-2022

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-09-2022
Application type:	Amendment
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	EUCTR2021-001716-29-NL
CCMO	NL81295.058.22