A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ANX1502 in Normal Healthy Volunteers

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PrimarySAD: - To evaluate the safety and tolerability of single ascending doses of ANX1502 in healthy participants.MAD: - To evaluate the safety and tolerability of multiple ascending doses of ANX1502 in healthy participants.SecondarySAD: - To...

Ethical review	Approved WMO
Status	Completed
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON53926

Source
ToetsingOnline

Brief title
CS0378-210342 Annexon

Condition

- Autoimmune disorders

Synonym
antibody-mediated autoimmune indications

Research involving

Human

Sponsors and support

Primary sponsor: Annexon Inc.
Source(s) of monetary or material Support: Annexon Inc.

Intervention

Keyword: pharmacodynamics, pharmakinetics, safety, tolerability

Outcome measures

Primary outcome

SAD part: Incidence and severity of treatment emergent adverse events (TEAEs) and clinically significant abnormalities in vital signs, clinical laboratory tests, and electrocardiogram (ECG) after single oral doses.

MAD part: Incidence and severity of TEAEs and clinically significant abnormalities in vital signs, clinical laboratory tests, and ECGs after multiple doses (over 14 days).

Secondary outcome

SAD part:

- Plasma ANX1502 and ANX1439 concentrations over time.

- ANX1502 and ANX1439 Day 1 plasma PK parameters (e.g., maximum observed plasma concentration [Cmax], observed time to Cmax [Tmax], area under the concentration-time curve [AUCs], terminal half-life [t1/2].

MAD part:

- Plasma ANX1502 and ANX1439 concentrations over time.

- ANX1502 and ANX1439 Day 1 and Day 14 plasma PK parameters (e.g., Cmax and

Tmax, AUCs and t1/2 minimum observed plasma concentration [Cmin], average

observed plasma concentration during multiple-dose administration [Cave],

%fluctuation, and accumulation ratio).

Study description

Background summary

Annexon is developing drugs that target complement component 1 complex (specifically, components C1q and C1s) in order to inhibit the activity of the classical complement pathway. The classical complement cascade is a part of the innate immune system that plays a significant role in the clearance of invading pathogens. The initiating molecule of the classical cascade is C1q which undergoes conformational change upon binding its target, resulting in activation of C1s protease and initiation of the rest of the classical complement cascade.
ANX1502 is a small molecule prodrug of ANX1439 which targets activated C1s serine protease. In vivo, and ANX1502 is rapidly converted to the pharmacologically active agent ANX1439, which as mentioned targets activated C1s thus inhibiting classical complement activation. ANX1439 does not affect complement activation through the lectin and alternate pathways, leaving the broader complement response intact.
The overall clinical development objective is to demonstrate the safety, tolerability, and efficacy of ANX1502 as a potential oral treatment of for antibody-mediated autoimmune diseases where complement activation is implicated in disease pathology.

Study objective

Primary
SAD:
- To evaluate the safety and tolerability of single ascending doses of ANX1502 in healthy participants.
MAD:
- To evaluate the safety and tolerability of multiple ascending doses of ANX1502 in healthy participants.

Secondary
SAD:
- To determine the single-dose pharmacokinetic (PK) profiles of ANX1502

(prodrug) and ANX1439 (active) in healthy participants
- To determine the effect of a high-fat meal (fed) on the PK profiles of ANX1502 and ANX1439 following a single dose of ANX1502 in healthy participants
MAD:
- To determine the steady-state PK profiles of ANX1502 (prodrug) and ANX1439 (active) in healthy participants

Study design

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study

Intervention

ANX1502 or matching placebo

Study burden and risks

Since the study is being executed in healthy volunteers, there are no anticipated benefits of the IMP. Please see the overall benefit risk in the CSP for further information.

Contacts

Public
Annexon Inc.

Sierra point Pkwy, Building C, 2nd Floor 1400
Brisbane CA 94005
US
Scientific
Annexon Inc.

Sierra point Pkwy, Building C, 2nd Floor 1400
Brisbane CA 94005
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Participants who are healthy as determined by medical evaluation including medical history, physical examination, vital signs assessments (including supine blood pressure, supine pulse rate, respiration rate, and temporal body temperature), single 12-lead ECG and laboratory tests.
- [MAD cohorts only] Must be willing to receive vaccinations for encapsulated bacteria.

Exclusion criteria

- Clinically significant infection (e.g., viral, bacterial, fungal, or mycobacterial) within 30*days prior to study intervention that required medical intervention (not including antibiotic prophylaxis)
- Clinically significant Screening values measured after 5 minutes of rest in a seated or semi-supine position include:
* Abnormal systolic blood pressure (< 90 or > 140 mmHg).
* Abnormal diastolic blood pressure (< 50 or > 90 mmHg).
* Body temperature (> 38°C).
* Respiration rate at rest (> 20 per minute).
* Clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions
- Has clinically significant laboratory abnormalities (at Screening) including:
* Serum creatinine > upper limit of normal (ULN).
* Estimated creatinine clearance of <80 mL/min as determined by estimated glomerular ratio [eGFR] (Cockroft Gault).
* Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) laboratory values > 1.5 x ULN.
* Total bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%)
- Known hepatic or biliary abnormalities (except for participants with Gilbert*s Syndrome who have serum bilirubin < 3 x ULN National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE v5.0] Grade 2, or asymptomatic gallstones).

- Has a clinically significant history or presence of ECG findings as judged by the Principal Investigator (PI) or designee at Screening, including:
* QT interval corrected for heart rate (QTc) >450 msec for male participants or >470 msec for female participants.
* Abnormal sinus rhythm (heart rate <40 bpm or > 100 bpm).
* Average QRS interval > 120 msec after being confirmed by manual over-read.
* Average PR interval > 220 msec.
* Resting bradycardia (ventricular rate [VR] < 45 beats per minute [bpm]) or tachycardia (VR > 90 bpm) on Screening ECG.
- An antinuclear antibodies (ANA) titer >= 1:160 at Screening.
- Has donated blood or plasma within 30 days prior to Screening or had a loss of whole blood of more than 500 mL within the 30 days prior to Screening, or receipt of a blood transfusion within one year prior to Screening
- Unable to consume a high-fat diet, if selected for the FE part of the study.
- Has experienced symptoms of acute illness or chronic disease within 14 days prior to Screening, or any disease or condition (medical or surgical) that, by the determination of the Investigator, might compromise interpretation of safety or PK data, or would place the participant at risk because of participation in the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-05-2022
Enrollment:	141
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Nap.
Generic name:	Nap.

Ethics review

Approved WMO Date:	25-04-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-05-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-01-2024
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-03-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-07-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2022-000594-21-NL
ClinicalTrials.gov	NCT05521269
CCMO	NL80646.056.22