A randomised, double-blind, placebo-controlled, ascending single and multiple dose first-in-human study to demonstrate the safety, tolerability and pharmacokinetics of ANXV administered as an intravenous infusion to healthy male subjects.

Published: 09-10-2020
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Part 1 SAD:Primary objective: To evaluate the safety and tolerability of single ascending doses of ANXV in healthy subjects.Secondary objective: To determine the PK profile of single ascending doses of ANXV in healthy subjects.Part 2 MAD:Primary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Retina, choroid and vitreous haemorrhages and vascular disorders
Study type	Interventional

Summary

ID

NL-OMON51171

Source
ToetsingOnline

Brief title
CS0356-200226

Condition

- Retina, choroid and vitreous haemorrhages and vascular disorders

Synonym
Retinal vein occlusion

Research involving
Human

Sponsors and support

Primary sponsor: Annexin Pharmaceuticals
Source(s) of monetary or material Support: Annexin Pharmaceuticals

Intervention

Keyword: pharmacokinetics, safety, tolerability

Outcome measures

Primary outcome

Part I:

Frequency, intensity and seriousness of adverse events (AEs)

Clinically significant changes in:

-ECG

-Telemetric recordings

-Vital signs (blood pressure, pulse, body temperature, respiratory rate, pulse

oximetry)

-Safety laboratory parameters

-Physical examinations

Incidence and titre of ADA to ANXV

Part II:

Frequency, intensity and seriousness of AEs

Clinically significant changes in:

-ECG

-Telemetric recordings

-Vital signs (blood pressure, pulse, body temperature, respiratory rate, pulse oximetry)

-Safety laboratory parameters

-Physical examinations

Incidence and titre of ADA to ANXV

Secondary outcome

Part I:

PK parameters (will be calculated if sufficient data are available):

-Area under the plasma concentration vs time curve from time zero extrapolated to infinity (AUCinf)

-AUC from time zero to time of last quantifiable analyte concentration (AUClast)

-Observed maximum concentration (Cmax)

-Time to Cmax (Tmax)

-Terminal slope of a semi-logarithmic concentration-time curve (*z)

-Terminal half life (T*)

-Clearance (CL)

-Volume of distribution (Vz)

-Dose proportionality after a single dose, based on AUC and Cmax

-Fraction excreted in urine (fe)

Part II:

PK parameters after first dose (will be calculated if sufficient data are available):

-AUClast

-Cmax

-Tmax

-*z

-T*

-CL

-Vz

-Dose proportionality

- Fraction excreted in urine (fe) (only cohort 3)

PK parameters after last dose:

-AUC during a dosage interval (tau) (AUCtau)

-Cmax

-Tmax

-*z

-T*

-CL

-Vz

-Vss

-Dose proportionality after multiple doses, based on AUC at steady state

(AUCtau) and Cmax

-Accumulation ratio

-Minimum plasma concentrations of ANXV on Day 5 (Cmin)

-Mean plasma concentrations of ANXV on Day 5 (Cmean)- Fraction excreted in urine (fe) (only cohort 3)

Study description

Background summary

ANXV is in development as a potential first-line treatment for patients with retinal vein occlusion (RVO). RVO is a debilitating, sight-threatening disease caused by an occlusion of the retinal vein. No registered treatment for acute resolution of RVO is available and there is a high unmet medical need to improve the blood flow to retina in the acute setting prior to the emergence of complications.
The proposed drug product ANXV contains human protein Annexin A5 produced by recombinant techniques in Escherischia Coli. As the endogenous Annexin A5, the recombinant protein specifically binds to a negative phospholipid-phosphatidylserine (PS) on cell membranes. ANXV ability to bind to PS has been confirmed by the Sponsor in vitro.
PS has been recently identified as a key molecule on RVO patients erythrocytes that is involved in formation of the retinal vein occlusion. On the basis of in vitro, ex vivo and in vivo pharmacology results, ANXV is expected to rapidly and focally bind to PS-carrying erythrocyte membranes, interfere with PS-dependent adherent cell-to-cell interactions at the site of occlusion, reduce the size of or remove the occlusive aggregate. Thus, ANXV holds potential to rapidly improve retinal blood supply, reduce the risk of blindness and provide other short-term and long-term benefits for RVO patients treated in the acute setting (as soon as possible after the diagnosis) and prior to the emergence of complications.

Study objective

Part 1 SAD:
Primary objective: To evaluate the safety and tolerability of single ascending doses of ANXV in healthy subjects.
Secondary objective: To determine the PK profile of single ascending doses of ANXV in healthy subjects.

Part 2 MAD:
Primary objective: To evaluate the safety and tolerability of multiple ascending doses of ANXV in healthy subjects.
Secondary objectives: To determine the PK profile of multiple ascending doses of ANXV in healthy subjects.

Study design

This is an adaptive, randomised, double-blind, single-centre, placebo-controlled phase I, first-in-human (FIH) study designed to evaluate the safety, tolerability and pharmacokinetics (PK) of single and multiple

intravenous dosing of ANXV in healthy male subjects.
This study is divided in 2 parts. Part I, Single Ascending Dose (SAD), will explore safety, tolerability and PK of single intravenous doses of ANXV. Part II, Multiple Ascending Dose (MAD), will explore safety, tolerability and PK of multiple intravenous doses of ANXV.
See section 9 of the CSP.

Intervention

intravenous doses of ANXV or 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 IB for further information.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Willing and able to give written informed consent for participation in the study.
Healthy male subject aged 18-60 years inclusive.
Body Mass Index (BMI) >= 18.0 and <= 30.0 kg/m2 and weight at least 50 kg and no more than 100 kg at screening.
Overtly healthy based on medical history, physical findings, vital signs, ECG and laboratory values at the time of screening, as judged by the Investigator.
Male subjects must be willing to use condom or be vasectomised or practice sexual abstinence to prevent pregnancy and drug exposure of a partner, and refrain from donating sperm from the date of dosing until 3 months after (last) dosing with the IMP.
Their female partner of child-bearing potential are expected to use contraceptive methods with a failure rate of < 1% to prevent pregnancy (combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD] or intrauterine hormone-releasing system [IUS]).

Exclusion criteria

History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject*s ability to participate in the study.
Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of IMP.
Malignancy within the past 5 years with the exception of in situ removal of basal cell carcinoma.
Any planned major surgery within the duration of the study.
Any positive result on screening for serum hepatitis B surface antigen (HbsAg), hepatitis C antibody and Human Immunodeficiency Virus (HIV).

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:	Recruitment stopped
Start date (anticipated):	21-12-2020
Enrollment:	68
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nap.
Generic name:	Nap.

Ethics review

Approved WMO Date:	09-10-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2021
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2021
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	EUCTR2020-004361-39-NL
CCMO	NL75226.056.20

Study results

Results posted: 22-11-2023

First publication
02-11-2023