Near-Infrared Fluorescence Molecular Imaging of ANXV-800CW to Visualize its Biodistribution in the Eyes of Patients Suffering from Retinal Vein Occlusion and Diabetic Retinopathy

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The primary objectives1. To assess the safety and tolerability of intravenous tracer administration of ANXV-800CW in up to three doses (0.5 mg, 1.0 mg, 2.0 mg flat dose) in patients with RVO and/or DR2. To determine the feasibility of molecular…

Ethical review	Approved WMO
Status	Pending
Health condition type	Ocular haemorrhages and vascular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52314

Source
ToetsingOnline

Brief title
ANXV-800CW visualization in RVO/ DR patients using fluorescence imaging

Condition

- Ocular haemorrhages and vascular disorders NEC

Synonym
retinal vein occlusion and diabetic retinopathy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Annexin Pharmaceuticals AB,Annexin Pharmaceuticals AB, Sweden

Intervention

Keyword: Annexin A5, Diabetic Retinopathy, Fluorescence molecular imaging, Retinal vein occlusion

Outcome measures

Primary outcome

To asses the safety and tolerability of intravenous administration of

ANXV-800CW (in 3 doses: 0.5 mg, 1.0 mg, 2.0 mg flat dose) in patient with

RVO/DR. This will be done by monitoring and evaluating whether (serious)

adverse events (S-)AEs) and suspected unexpected serious adverse reactions

(SUSARs) have occurred. These are defined as clinically significant changes in:

- Vital signs: blood pressure, heart rate, respiratory rate, body temperature

- Safety laboratory parameters such as incidence and titre of Anti-Drug

Antibodies ADA to ANXV

To asses the feasibility of fluorescent imaging for visualization/targeting of

ANXV-800CW in 3 doses (0.5 mg, 1.0 mg, 2.0 mg flat dose) in RVO/DR patients,

using a Near-Infrared (NIR) fluorescent imaging system. For this the

target-to-background ratio will be determined of the fluorescent signal by

using rbitrary Units (AUs)right before intravenous injection of ANXV-800CW and

at 5 minutes, 10 minutes, 20 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours

and 4 hours following administration.

Secondary outcome

To asses the pharmacokinetic profile of ANXV-800CW (3 doses: 0.5 mg, 1.0 mg, 2.0 mg flat dose) in patients with RVO/DR. This will be done, 5, 10, 20,30 minutes, 1 hour, 1.5 hours, 2 hours and 4 hours post administration:

- 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 if several dose levels are investigated

In addition, this study will look at the PS availability, as measured with Flow Cytometry right before and after ANXV-800CW administration.

Study description

Background summary

Based on population-based studies, approximately 16.4 million people are diagnosed with retinal vein occlusion (RVO) worldwide. These studies have also

shown that the prevalence of RVO is between 0.40-2.2%. RVO is caused by an abnormal blood flow in the retina, as a result of venous occlusion (thrombosis). The severity of RVO depends on the site of the thrombosis. The site of the thrombosis determines if the retina is partial or completely affected by complications such as partial or complete blindness. The nature of the occlusion formed in RVO patients has been debated. Notably, attempts to treat RVO with classical antithrombotic or antiplatelet drugs have been largely unsuccessful and are not a part of standard of care. Current treatment strategies are based on the prevention of subsequent complications by inhibiting the over-expression of Vascular Endothelial Growth Factor (VEGF), inflammation and ischemia, using anti-VEGF therapeutics, corticosteroids and laser therapy. There is currently no effective treatment modality for the underlying cause of RVO.

ANXV is in development as a potential first-line treatment for patients with retinal vein occlusion (RVO). The proposed drug product ANXV contains human protein Annexin A5 produced by recombinant techniques in Escherichia 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 subsidizing party in vitro.

Recently, phosphatidylserine (PS) has been identified as a key molecule on erythrocytes derived from patients with RVO and Annexin A5 has been demonstrated to reduce the PS mediated aggregation and adhesion and aggregation to vascular endothelium seen by the abnormal RVO-erythrocytes, providing indirect proof of a potential to impact the venous 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 cell membranes, interfere with PS-dependent adherent cell-to-cell interactions at the site of occlusion, reduce the size of or remove the occlusive aggregate.

In addition, Annexin-A5 is able to interfere with prothrombinase by acting on coagulation factors, such as IXa-X-VIIa and Xa-prothrombin-Va. Moreover, Annexin A5 is able to form a shield over PS on the membrane of the blood platelets, red blood cells and endothelial cells. This layer reduces the mobility of prothrombin and down-regulates tissue factors as coagulation factor Xa. Combined, it causes 99% of the prothrombinase activity to be reduced, therefore thrombin cannot be formed. Consequently, ANXV is expected to have a targeted anticoagulation/ antithrombotic effect in RVO.

RVO is also associated with localized inflammation contributing to the macular oedema and neo-vascularization. As a potential additional mode of action, ANXV is known to reduce vascular inflammation in vivo. Lastly, in RVO, multiple cells including the vascular endothelial cells are stressed and damaged. Annexin A5 has been demonstrated to heal damaged cells by stabilizing and supporting the re-alignment of phospholipids in the cell membrane.

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.
The current near-infrared fluorescent diagnostic imaging study is aimed at real-time visualization of Good Manufacturing Practice (GMP) produced fluorescent-labelled ANXV-800CW in the eye of patients with RVO, determining the binding of the labelled compound at the site of the venous occlusion.

Also, in the pathophysiology of DR, PS is expected to play a role. There is both preclinical and clinical evidence that supports the hypothesis of the usefulness of Annexin A5 in patients with DR. Research has shown that PS exposure on platelets and monocytes was higher in proliferative DR than in non-proliferative DR patients or healthy subjects. In addition, Annexin A5 imaging was used successfully in animal models of Diabetes Mellitus aimed at monitoring the efficacy of therapeutic agents designed to suppress ischemia-induced apoptosis. At least one imaging technology DARC (Detection of Apoptosing Retinal Cells), has investigated the visualization of single retinal neurons undergoing apoptosis by using fluorescently labeled Annexin A5 and confocal scanning laser ophthalmoscopy in patients with glaucoma and in animal models of other eye diseases. In DR, Annexin A5 can thus be useful for the targeting of apoptotic PS-expression, which is expected to be present in the affected eye due to retinal ischemia.

Since RVO is a rare disease and inclusion of RVO patients in the study is cumbersome, we will use Diabetic retinopathy as an additional patient population with PS expression in the eye. By investigating the uptake of ANXV in affected retinal vessels, the proof-of-concept of PS targeting with ANXV can be established.

Study objective

The primary objectives
1. To assess the safety and tolerability of intravenous tracer administration of ANXV-800CW in up to three doses (0.5 mg, 1.0 mg, 2.0 mg flat dose) in patients with RVO and/or DR
2. To determine the feasibility of molecular fluorescence imaging in the retina of patients in up to three doses (0.5 mg, 1.0 mg, 2.0 mg flat dose) with RVO and/or DR, using ANXV-800CW for visualizing biodistribution/targeting in the eye using a Near- Infrared (NIR) fluorescence imaging system.

Secondary objectives
1. To determine the pharmacokinetic profile of ANXV-800CW in up to three doses (0.5 mg, 1.0 mg, 2.0 mg flat dose) in patients with RVO and/or DR.
2. To determine phosphatidylserine availability as measured by flow cytometry in whole blood before and after ANXV-800CW administration.

Study design

non-randomized, non-blinded, prospective, mono-center safety/ feasibility dose optimization study

Intervention

All patients will undergo a standard of care ophthalmological work-up to establish the diagnosis of RVO/DR: Best Corrected Visual Acuity (BCVA), Tonometry, slit lamp biomicroscopy, fundoscopy, Optical Coherence Tomography (OCT), Optical Coherence Tomography Angiography (OCT-A). In the context of this study, Fluoresceine Angiography (FA) will be added to the ophthalmological work-up for all patients. Furthermore, the patients will receive a systemic single-dose injection of ANXV-800CW as part of a optimization study (either 0.5 mg, 1.0 mg or 2.0 mg), followed by NIR retinal fluorescence imaging. All procedures will be performed on both eyes, the affected eye and the non-affected eye.

Study burden and risks

The nature of participating to the study for the individual participant is related to the injection of the fluorescent tracer ANXV-800CW and the additional imaging procedures related to the study which are not standard of care. The tracer is composed of the targeting moiety ANXV, a recombinant human Annexin A5. Annexin A5s, albeit not the specific moiety ANXV, but with similar binding properties has a known pharmacological profile from being used as imaging agent in healthy volunteers and patients in nuclear molecular imaging. Moreover, safety data are available of the systemic injection of ANXV in healthy volunteers, a study with no evidence of drug related (S-)AEs or SUSARs using the same dose-range intended for ANXV-800CW. As part of the in- and exclusion criteria, kidney function is taken into account which decreases the risk of safety issues. As mentioned, participants need to undergo some diagnostic procedures besides the standard-of-care (SOC) for RVO/DR, which creates an additional burden of time-investment may and impact patients with RVO/DR. The imaging procedures are regarded a minimal risk as they are already standard procedures within the diagnostic work-up of patients with complicated RVO/DR. Blood sampling form superficial veins is not SOC and as such can pose a risk of pain, hematoma and syncope related to the blood sampling. Patients in the study are not expected to have a direct benefit, but it cannot be excluded. The results of the study will support the anticipated dosing-range of ANXV for treatment of RVO, (in the range of 0.5 to 2.0 mg), by the read-out of side-specific targeting in the eye and the causing mechanism, which is thrombosis. Furthermore, the results may support a development of an imaging tool for selection of potential responders, prior to installment of ANXV treatment in patents with RVO to confirm their eligibility for targeted ANXV treatment. In conclusion, individual patients participating in the study may

serve the patient RVO group benefit for creating insight in the targeting of ANXV in RVO.

Since RVO is a rare disease and inclusion of RVO patients in the study is cumbersome, we will use Diabetic retinopathy as an additional patient population with PS expression in the eye. By investigating the uptake of ANXV in affected retinal vessels, the proof-of-concept of PS targeting with ANXV can be established.

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

RVO:
- Willing to adhere to the prohibitions and restrictions specified in this

protocol.
- Capable of giving signed informed consent (voluntarily), indicating that the patient understands the purpose and procedures required for the study and is willing to comply with the requirements and restrictions listed in the informed consent form and in this protocol.
- Patients aged 18-85 years inclusive at moment signing informed consent form.
- Established (sub) acute Retinal Vein Occlusion
o Branch retinal vein occlusion (BRVO) or Central retinal vein occlusion (CRVO)
- BMI >= 18.0 and <= 35.0 kg/m2
- Overtly healthy based on medical history, physical findings, vital signs, ECG at the time of screening, as judged by the Investigator.
o Note: one retest of vital functions and ECG is allowed within the screening window
- No clinically significant laboratory abnormalities as determined by the investigator
o Note: one retest of lab tests is allowed within the screening window
- Female patients should fulfil one of the following criteria:
o At least 1 year post-menopausal (amenorrhea >12 months and/or follicle-stimulating hormone >30 mIU/mL) at screening;
o Surgically sterile (bilateral oophorectomy, hysterectomy, or tubal ligation);
o Women >45 years of age without a child wish, who agree to use an adequate form of contraceptives during the study and whom have not the intention to become pregnant anymore. In the case of an unlikely pregnancy, they accept the possible maternal/ fetal risk of participation in the study
- Male subjects who are sexually active with a female partner of childbearing potential must agree to the use of an effective method of birth control, and must not donate sperm, until 3 months after administration of ANXV-800CW.

DR:
- Willing to adhere to the prohibitions and restrictions specified in this protocol.
- Capable of giving signed informed consent (voluntarily), indicating that the patient understands the purpose and procedures required for the study and is willing to comply with the requirements and restrictions listed in the informed consent form and in this protocol.
- Patients aged 18-85 years inclusive at moment signing informed consent form.
- Patients should be graded as one of the following:
o Diabetic retinopathy grade R2 pre-proliferative
o Diabetic retinopathy grade R3 proliferative
o Diabetic maculopathy grade M1
- BMI >= 18.0 and <= 35.0 kg/m2
- Overtly healthy based on medical history, physical findings, vital signs, ECG at the time of screening, as judged by the Investigator.
o Note: one retest of vital functions and ECG is allowed within the screening window
- No clinically significant laboratory abnormalities as determined by the investigator

o Note: one retest of lab tests is allowed within the screening window
- Female patients should fulfil one of the following criteria:
o At least 1 year post-menopausal (amenorrhea >12 months and/or follicle-stimulating hormone >30 mIU/mL) at screening;
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- Male subjects who are sexually active with a female partner of childbearing potential must agree to the use of an effective method of birth control, and must not donate sperm, until 3 months after administration of ANXV-800CW.

Exclusion criteria

RVO:
General:
- Behavioral or cognitive impairment or psychiatric disease that in the opinion of the investigator affects the ability of the patient to understand and cooperate with the study protocol
- Deprived of freedom by an administrative or court order or in an emergency setting.
- Insufficient venous access for the study procedures.
- Close affiliation with the investigator; e.g. a close relative of the investigator,
dependent person (e.g. employee or student), employee of the department of Ophthalmology of the UMCG, TRACER or affiliates
- Any finding in the medical examinations or medical history giving, in the opinion of the Investigator, reasonable suspicion of a disease or condition that makes treatment with the investigational drug unadvisable, or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
- Participation in an interventional clinical study within 30 days prior to screening visit (visit 1) that involved treatment with any drug (excluding vitamins and minerals) or medical device
- Current alcohol/illicit drug abuse or addiction: history or evidence of current drug use or addiction (positive urine drug screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, or opiates) or excessive use of alcohol at screening.
- Positive blood for safety: positive blood test on Hepatitis B, Hepatitis C and HIV.

Medical conditions
- Eye disease that significantly interferes with fundus examinations in one or both eyes

- Dilatation of the pupil < 5 mm in the study eye
- Ocular inflammation (including trace or more severe) or conjunctivitis at screening, or history of uveitis in either eye
- Only one functional eye
- Current use of any medication that might have effect on the coagulation cascade, hemostasis, and platelets.
o Note: the use of platelet aggregation inhibitors, such as acetyl salicylic acid or its equivalents, is allowed.
o Note: the use of vitamin K antagonists is allowed given that the INR is stable between 1-3 over the last 6 months before inclusion.
- History of significant bleeding (gross haematuria, haemoptysis, gastrointestinal tract bleeding)
- Evidence or history of a hypercoagulable state (e.g. shortened APTT).
- Document history of autoimmune disease with anticipated presence of potentially pathogenic Annexin A5 antibodies, e.g. antiphospholipid syndrome, systemic lupus erythematosus or systemic sclerosis.
- Confirmed thalassemia (e.g sickle cell disease)
- Uncontrolled arterial hypertension, defined as systolic blood pressure > 160 mmHg or
diastolic blood pressure > 100 mmHg. One retest of vital functions is allowed within the screening window.
- Cardiac impairment with an estimated LVEF < 35 % Prolonged QTcF (>450 ms), cardiac arrhythmias or any clinically significant abnormalities in the resting ECG at the time of screening, as judged by the investigator
- History of or a currently active hepatic or biliary disease
- History of or a currently active neurological disease
- eGFR (based on plasma-creatinine) outside of normal range at screening or known renal impairment (<=40 mL/min).
- Any abnormalities in the vital signs of the patient, as judged by the investigator, as a result of which the patient cannot participate
- Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the administration of IMP.
- Current evidence or history of bacterial, viral or fungal infections within 7 days before ANXV-800CW administration as judged by the Investigator.
o T > = 38.0°C or lab confirmed viral/bacterial/fungal infection (PCR)) or symptoms suggestive of an infection)
- Any planned major surgery within the duration of the study (until visit 3), with the exception of any emergency surgeries.
- Any laboratory test which is abnormal, and which is deemed by the Investigator(s) to be clinically significant
- A history of anaphylaxis, history of allergic reaction(s), known allergy to one of the drugs or excipients administered as part of this study. Mild allergies without angio-edema or treatment need can be acceptable if deemed not to be of clinical significance (including but not limited to allergy to animals or mild seasonal hay fever)
- Current diagnosis of asthma or reactive airway disease associated with exercise for which medication is used

Prior therapy
- Any prior systemic anti-VEGF treatment or intravitreal (IVT) anti-VEGF treatment in the affected eye within a period of 3 months prior to start of the study
- Any prior intraocular steroid injection in the affected eye within a period of 3 months prior to start of the study
- Any prior grid or focal laser photocoagulation within 500 microns of the foveal center
or any prior panretinal photocoagulation (PRP) in the affected eye
- Any intraocular eye surgery in the affected eye within a period of 3 months prior to start of the study
- Yttrium-Aluminum-Garnet laser treatment performed within 28 days before screening,
in the affected eye

DR:
General:
- Behavioral or cognitive impairment or psychiatric disease that in the opinion of the investigator affects the ability of the patient to understand and cooperate with the study protocol
- Deprived of freedom by an administrative or court order or in an emergency setting.
- Insufficient venous access for the study procedures.
- Close affiliation with the investigator; e.g. a close relative of the investigator,
dependent person (e.g. employee or student), employee of the department of Ophthalmology of the UMCG, TRACER or affiliates
- Any finding in the medical examinations or medical history giving, in the opinion of the Investigator, reasonable suspicion of a disease or condition that makes treatment with the investigational drug unadvisable, or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
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- History of or a currently active hepatic or biliary disease
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- Any prior intraocular steroid injection in the affected eye within a period of 3 months prior to start of the study
- Any prior grid or focal laser photocoagulation within 500 microns of the foveal center
- or any prior panretinal photocoagulation (PRP) in the affected eye within a period of 3 months prior to start of the study
- Any intraocular eye surgery in the affected eye within a period of 3 months prior to start of the study
- Yttrium-Aluminum-Garnet laser treatment performed within 28 days before screening,
in the affected eye

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-04-2021
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Annexin A5
Generic name:	Annexin A5

Ethics review

Approved WMO

Date:	17-09-2021

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2022
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	EUCTR2021-000866-13-NL
CCMO	NL77192.056.21