REPOTRIAL

An in silico-based approach to improve the efficacy and precision of drug REPurpOsing TRIALs for a mechanism-based patient cohort with predominant cerebro-cardiovascular phenotypes

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777111.

Deliverable
D3.7 "Publication on study design, study protocol and start: pilot study 1: STROKE"

Work Package
WP3 "Clinical validation of in-silico trial prediction"

Disclaimer

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 777111. Any dissemination of results reflects only the author's view and the European Commission is not responsible for any use that may be made of the information it contains.

Copyright message

© REPO-TRIAL Consortium, 2023
This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both. Reproduction is authorised provided the source is acknowledged.

Document information

Grant Agreement Number: 777111				**Acronym: REPO-TRIAL**
Full title	An in silico-based approach to improve the efficacy and precision of drug REPurpOsing TRIALs for a mechanism-based patient cohort with predominant cerebro-cardiovascular phenotypes			
Topic	In-silico trials for developing and assessing biomedical products			
Funding scheme	RIA - Research and Innovation action			
Start Date	1 February 2018	**Duration**	72 months	
Project URL	https://repo-trial.eu/			
EU Project Officer	Dusan Sandor, Programme Officer, European Commission			
Project Coordinator	Prof. Dr. Harald H.H.W. Schmidt, Universiteit Maastricht (UM)			
Deliverable	D3.7			
Work Package	WP3			
Date of Delivery	**Contractual**	30.09.2023	**Actual**	16.11.2023
Nature	R	**Dissemination Level**	PU	
Lead Beneficiary	4 - UKE			
Responsible Author(s)	PD Dr. med. Benedikt Frank (UKE)			
Keywords	Publication on study design, study protocol and start			

History of changes

Version	Date	Contributions	Contributors (name and institution)
V0.1	10/11/2023	First draft	Benedikt Frank (UKE)
V1	13/11/2023	Final version	Benedikt Frank (UKE)
V1	16/11/2023	Approval	Harald Schmidt (UM)
V1	16/11/2023	Submission	Vanessa Köhler (concentris)

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 777111.

Table of Content

1 Objectives of the deliverable based on the Description of Action (DoA) 5
2 Attachment 5

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 777111.

1 Objectives of the deliverable based on the Description of Action (DoA)

This deliverable report contains the study details and table view of the publication “Networked Drug REpurposing for Mechanism-based neuroPrOtection in Acute Ischaemic STROKE (REPO-STROKE II)” which was first posted on March 09, 2023 on ClinicalTrials.gov as attachment.

2 Attachment

- Study Details - “Networked Drug REpurposing for Mechanism-based neuroPrOtection in Acute Ischaemic STROKE (REPO-STROKE II)”
- Table View - “Networked Drug REpurposing for Mechanism-based neuroPrOtection in Acute Ischaemic STROKE (REPO-STROKE II)”

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 777111.

The U.S. government does not review or approve the safety and science of all studies listed on this website.
Read our full disclaimer for details.

ClinicalTrials.gov is a website and online database of clinical research studies and information about their results. The National Library of Medicine (NLM) maintains the website. **The study sponsor or investigator is solely responsible for ensuring that study information you post to ClinicalTrials.gov is accurate, complete, and consistent with the scientific literature, and accuracy** of any study they list.

Before joining a study, talk to your health care professional about possible risks and benefits. To learn more about taking part in studies, read Learn About Studies.

RECRUITING

Networked Drug REpurposing for Mechanism-based neuroPrOtection in Acute Ischaemic STROKE (REPO-STROKE II)

ClinicalTrials.gov ID ▶ NCT05921146
Sponsor ▶ Maastricht University
Information provided by ▶ Maastricht University (Responsible Party)
Last Update Posted ▶ 2023-10-19

+ Expand all content | − Collapse all content

Study Details | Table View | No Results Posted | Record History

On this page
- Study Overview
- Contacts and Locations
- Participation Criteria
- Study Plan
- Collaborators and Investigators
- Publications
- Study Record Dates
- More Information

Study Overview

Brief Summary

A prospective therapy proposed to be evaluated in this trial, consisting of three already registered compounds with a validated disease mechanism and with known safety profiles, targets key proteins in the dysregulated signal network in stroke, and is expected to synergistically result in post-stroke blood-brain barrier stabilization and neuroprotection. The synergistic mode of action will allow for low doses and is expected to reduce possible side effects while maintaining maximal efficacy.

Detailed Description

There is a high need for new drugs & novel approaches for neuroprotection in stroke treatment.

Pre-clinically, data presented in silico predicted drug targets and pharmacological principles all belonging to the same signal network were validated at the preclinical level to be causally relevant in stroke and thus hold promise for the first-in-class mechanism-based, neuroprotective treatment in acute ischemic stroke:

1. NADPH oxidase type 4 and 2 (NOX4, NOX2), members of a reactive oxygen radical (ROS) forming enzyme family being either upregulated during hypoxia or activated by high post-reperfusion calcium influx causing vascular levels of ROS and thereby blood-brain barrier (BBB) breakdown and neuronal damage, respectively. Both NOX4 and NOX2 are also known to be hypoxia-induced (hypoxia-inducible factor 1 alpha-dependent) and produce reaction quantities of ROS, which are further amplified by chemically interacting with NADPH oxidase-derived ROS, forming and even more toxic peroxynitrite and which can be prevented by NOS inhibitors (NOSIs).
2. Soluble guanylate cyclase (sGC), an enzyme, which forms the BBB stabilizing and neuroprotective second messenger cGMP (cyclic guanosine 3',5'-monophosphate) and is inactivated by oxidative stress (sGC (Fe-peroxynitrite). Moreover any remaining sGC is less activated by NO because NO is scavenged by ROS and detoxified into peroxynitrite. Thus, cGMP formation is greatly reduced in strokes, which can be reversed by sGC modulators which increase the sensitivity of both sGC and apo-sGC in an NO-independent manner and thereby reinstall cGMP formation, BB closure and neuroprotection.

Different representatives of the drug classes of NADPH oxidase inhibitors (NOXIs), nitric oxide synthase inhibitors (NOSIs), and soluble guanylate cyclase modulators were identified and shown to be highly effective when given alone in different animal experimental and in vitro human models, underlining the relevance of the identified signal network in stroke. The combination of targeting the two decisive, and ROS and sGC of belong to the same disease modules, an innovative combined, so-called network pharmacology approach is proposed, i.e., a combination of 3 already registered compounds with a validated disease mechanism: the sGC activator cinaciguat, the NOX1 inhibitor propiflavoneol, and the NOX inhibitor peptide vonapanitase.

Cinaciguat is an sGC stimulator currently approved and marketed for pulmonary hypertension. Post-reperfusion therapy with cinaciguat, increased cGMP formation and therefore leads to direct vasodilation and improved blood-brain barrier function and neuroprotection. Propiflavoneol is already marketed for the treatment of various subtypes of hypertrophication, has been identified as a new member of the class of potent and effective NOX1 inhibitors. Pre-clinically, post-reperfusion treatment with propiflavoneol significantly reduced infarct volume in brain ischemia mice models compared to non-treated animals (pre-clinical in house data, unpublished). Peptavonex is already marketed as an intranasal spray for the treatment of Parkinson's disease and has been identified as a new member of the same drug class, and significantly reduced infarct size in acute ischemic stroke mice models.

In summary, the combination therapy proposed to be evaluated in this trial, consisting of already registered compounds with a validated disease mechanism and with known safety profiles, targets key proteins in the dysregulated signal network in stroke, and is expected to synergistically result in post-stroke blood-brain barrier stabilization and neuroprotection. The synergistic mode of action will allow for low doses and is expected to reduce possible side effects while maintaining maximal efficacy.

→ Show less

Official Title

Networked Drug REpurposing for Mechanism-based neuroPrOtection in Ischaemic **STROKE (REPO-STROKE II)**

Conditions ▶

Ischaemic Stroke, Acute

Intervention / Treatment ▶

- Drug: Rivoxiguat
- Drug: Propiflavoneol
- Drug: Peptavonex

Other Study ID Numbers ▶

- REPO-STROKE II
- 2019-004264-31 (EudraCT Number)

Study Start (Actual) ▶	2022-09-05
Primary Completion (Estimated) ▶	2024-02-29
Study Completion (Estimated) ▶	2024-04-30
Enrollment (Estimated) ▶	28
Study Type ▶	Interventional
Phase ▶	Phase 2
Study Design ▶	Allocation: Randomized Intervention Model: Parallel Assignment Primary Purpose: Treatment Masking: Triple (Participant, Investigator, Outcome Assessor)
Arms ▶	3
Accepts Healthy Volunteers	No

Resource links provided by the National Library of Medicine NIH NLM

Contacts and Locations

This section provides the contact details for those conducting the study and information on where this study is being conducted.

Study Contact ▶

Name: Harald Schmidt, MD PhD
Phone Number: +31455081427
Email: h.schmidt@maastrichtuniversity.nl

Germany

Maastricht University Medical Center
Maastricht, Limburg, 6229 HX
Principal Investigator: Gerard Hermanus Jacobus Hermanus Drummen, Department of Neurology
Contact: Benedikt Frank, Phe, Msc, Dr.
Principal Investigator: Benedikt Frank, Dr. rer. nat. Dr. med. habil. Dr. phil. nat. habil. Dr. rer. nat. habil. Dr. rer. nat. habil. Dr. rer

The U.S. government does not review or approve the safety and science of all studies listed on this website.

Read our full disclaimer for details.

ClinicalTrials.gov is a website and online database of clinical research studies and information about their results. The National Library of Medicine (NLM) maintains the website. **The study sponsor or investigator submits information** about their study to ClinicalTrials.gov and **is responsible for the safety, science, and accuracy** of any study they list.

Before joining a study, talk to your health care professional about possible risks and benefits. To learn more about taking part in studies, read Learn About Studies.

RECRUITING

Networked Drug REpurposing for Mechanism-based neuroPrOtection in Acute Ischaemic STROKE (REPO-STROKE II)

ClinicalTrials.gov ID NCT05762146

Sponsor Maastricht University

Information provided by Maastricht University (Responsible Party)

Last Update Posted 2023-10-19

Study Details | Table View | No Results Posted | Record History

On this page
- Trial Contacts
- Study Record Dates
- Outcome Measures
- Trial Description
- Recruitment Information
- Administrative Information

Trial Contacts

Contacts ICMJE	1. Contact: Harald Schmidt, MD PhD Phone Number: +31433881421 Email Address: h.schmidt@maastrichtuniversity.nl

Study Record Dates

First Submitted ICMJE	2022-08-23
First Posted ICMJE	2023-03-09
Last Update Posted	2023-10-19
Last Verified	2023-10

Outcome Measures

Change History	See all versions of this study
Primary (Current) ICMJE (Submitted: 2023-02-27)	• SICH as per ECASS III [Time Frame: 30 days] ◦ Frequency of symptomatic intracranial hemorrhages as per ECASS III
Primary (Original) ICMJE	Same as current

Secondary (Current) ICMJE
(Submitted: 2023-02-27)
	• SICH as per Heidelberg Bleeding Classification [Time Frame: 30 days]
	  ◦ Frequency of symptomatic intracranial hemorrhages as per Heidelberg Bleeding Classification
	• SICH as per SITSMOST [Time Frame: 30 days]
	  ◦ Frequency of symptomatic intracranial hemorrhages as per SITSMOST
	• SICH as per NINDS [Time Frame: 30 days]
	  ◦ Frequency of symptomatic intracranial hemorrhages as per NINDS
	• Mortality [Time Frame: 30 days]
	  ◦ Frequency of all cause mortality
	• SAE [Time Frame: 30 days]
	  ◦ All (S)AEs considered related to the triple combination therapy
	• Duration of hospital stay [Time Frame: 30 days]
	  ◦ Time from randomization to discharge
	• Duration of intensive care unit (ICU) stay [Time Frame: 30 days]
	  ◦ Period during which the patient stayed at a ward with capacity for mechanical ventilation
	• Duration of invasive mechanical ventilation [Time Frame: 30 days]
	  ◦ in hours
	• Duration of non-invasive mechanical ventilation [Time Frame: 30 days]
	  ◦ in hours
	• Change of initial 'volume of hypoperfusion' [Time Frame: 5 days]
	  ◦ Change in "ml" of volume of hypoperfusion in initial Computed Tomography Perfusion (CTP) to final 'volume of infarct core' as assessed through follow-up Magnetic Resonance Imaging (MRI).
	• Change of initial 'volume of infarct core' [Time Frame: 5 days]
	  ◦ Change in "ml" of infarct core of initial Computed Tomography Perfusion (CTP) to final 'volume of infarct core' as assessed through follow-up Magnetic Resonance Imaging (MRI).
	• mRS [Time Frame: 30 days]
	  ◦ Shift analysis of mRS
	• NIHSS change [Time Frame: 5 days]
	  ◦ Change from baseline in National Institute of Health Stroke Scale (NIHSS) score

Secondary (Original) ICMJE	Same as current
Other Pre-specified (Current)	Not provided
Other Pre-specified (Original)	Not provided

Trial Description

Brief Title ICMJE	Networked Drug REpurposing for Mechanism-based neuroPrOtection in Acute Ischaemic **STROKE**
Official Title ICMJE	Networked Drug REpurposing for Mechanism-based neuroPrOtection in Ischaemic **STROKE** (**REPO-STROKE** IIa)
Brief Summary	A combination therapy proposed to be evaluated in this trial, consisting of three already registered compounds with a validated disease mechanism and with known safety profiles, targets key proteins in the dysregulated signal network in stroke, and is expected to synergistically result in post-stroke blood-brain barrier stabilization and neuroprotection. The synergistic mode of action will allow for low doses and is expected to reduce possible side effects while maintaining maximal efficacy
Detailed Description	There is a high need for new drugs & novel approaches for neuroprotection in stroke treatment. Pre-clinically, three interrelated in silico predicted drug targets and pharmacological principles all belonging to the same signal network were validated at the preclinical level to be causally relevant in stroke and thus hold promise for the first-in-class mechanism-based, curative neuroprotective therapy of an ischemic stroke: 1. NADPH oxidase type 4 and 5 (NOX4, NOX5), members of a reactive oxygen radical (ROS) forming enzyme family being either upregulated during hypoxia or activated by high post-reperfusion calcium influx causing unphysiological high levels of ROS and thereby blood-brain barrier (BBB) breakdown and neuronal damage, which can be prevented by NOX inhibitors (NOXi). 2. Nitric oxide (NO) synthase type 1 (NOS1), a neuronal signaling enzyme, which in stroke is hyperactivated (excitotoxicity) and produces neurotoxic quantities of NO, which are further toxified by chemically interacting with NADPH oxidase-derived ROS, forming and even more toxic peroxynitrite and which can be prevented by NOS inhibitors (NOSi) 3. Soluble guanylate cyclase (sGC), an enzyme, which forms the BBB stabilizing and neuroprotective second messenger, cyclic GMP (cGMP), but upon stroke is oxidatively damaged to a heme-free apo sGC (by peroxynitrite). Moreover, any remaining sGC is less activated by NO, because NO is scavenged by ROS and deviated into peroxynitrite. Thus, cGMP formation is greatly reduced in stroke, which can be reversed by sGC modulators which increase the activity of both sGC and apo-sGC in an NO-independent manner and thereby reinstall cGMP formation, BB closure and neuroprotection. Different representatives of the drug classes of NADPH oxidase inhibitors (NOXi), nitric oxide synthase inhibitors (NOSi), and soluble guanylate cyclase modulators were identified and shown to be highly effective when given alone in different small animal experimentation and in vitro human models. However, since all single target approaches in stroke have so far failed in clinical development during the last decades, and NOS, NOX and sGC all belong to the same disease module, an innovative combined, so-called network pharmacology approach is proposed, i.e., a combination of 3 already registered compounds with a validated disease mechanism: the sGC activator riociguat, the NOS1 inhibitor propylthiouracil, and the NOX inhibitor perphenazine. Riociguat is an sGC stimulator currently approved and marketed for pulmonary hypertension. Post-reperfusion therapy with riociguat, increased cGMP formation and therefore leads to direct neuroprotection and reduced infarct volume in a stroke animal model. Propylthiouracil is already marketed for the treatment of various subtypes of hyperthyroidism and has been identified as a new member of the class of potent and effective NOS1 inhibitors. Pre-clinically, post-reperfusion treatment with propylthiouracil significantly reduced infarct volume in brain ischemia mice models compared to non-treated animals (pre-clinical in-house data, unpublished). Perphenazine is already marketed as an antiemetic and antipsychotic, has the best NOX inhibitory characteristics compared to other compounds of the same drug class, and significantly reduced infarct size in acute ischemic stroke mice models. In summary, the combination therapy proposed to be evaluated in this trial, consisting of already registered compounds with a validated disease mechanism and with known safety profiles, targets key proteins in the dysregulated signal network in stroke, and is expected to synergistically result in post-stroke blood-brain barrier stabilization and neuroprotection. The synergistic mode of action will allow for low doses and is expected to reduce possible side effects while maintaining maximal efficacy.
Study Type ICMJE	Interventional
Study Phase ICMJE	Phase 2
Study Design ICMJE	Allocation: Randomized Interventional Model: Parallel Assignment Interventional Model Description: This is a Prospective Randomized Open-label Blinded End-point (PROBE) trial evaluating safety and efficacy of a triple combination therapy of riociguat, propylthiouracil, and perphenazine, administered orally in addition to standard of care treatment in patients with disabling acute ischemic stroke. Patients will be randomly assigned to the triple combination therapy group or the control group in a 3:1 ratio: Masking: Single (Outcomes Assessor) Masking Description: This is a Prospective Randomized Open-label Blinded End-point (PROBE) trial Primary Purpose: Treatment
Condition ICMJE	• Ischemic **Stroke**, Acute

Intervention ICMJE	• Drug: Riociguat
	  ◦ Riociguat is an sGC stimulator currently approved and marketed for pulmonary arterial hypertension.
	  ◦ Other Names:
	    ▪ Adempas
	• Drug: Propylthiouracil
	  ◦ Propylthiouracil, already marketed for the treatment of various subtypes of hyperthyroidism, has been identified as a new member of the class of potent and effective neuronal nitric oxide synthase (NOS1) inhibitors
	  ◦ Other Names:
	    ▪ Propycil
	• Drug: Perphenazine
	  ◦ Perphenazine, already marketed as an antiemetic and antipsychotic drug, presents the best NADPH oxidase (NOX) inhibitory characteristics compared to other compounds of the same drug class.
	  ◦ Other Names:
	    ▪ Perphenazin neuraxpharm

Study Arms ICMJE	• Experimental: Riociguat +Propylthiouracil +Perphenazine
	  ◦ Triple combination therapy group:
	    ◦ each patient in this group will receive two doses (8 +/- 2 hours between doses) of orally administered combination therapy of riociguat, propylthiouracil, and perphenazine, in addition to standard of care.
	  ◦ Interventions:
	    ▪ Drug: Riociguat
	    ▪ Drug: Propylthiouracil
	    ▪ Drug: Perphenazine
	• No Intervention: standard of care
	  ◦ Control group: each patient in this group will receive only standard of care

Publications *	Not provided

* Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.

Recruitment Information

Recruitment Status ICMJE	Recruiting
Enrollment (Estimated) ICMJE (Submitted: 2023-02-27)	28
Original Enrollment (Estimated) ICMJE	Same as current
Study Start Date (Actual) ICMJE	2022-09-05
Primary Completion Date (Estimated)	2024-02-29 (Final data collection date for primary outcome measure)
Study Completion Date (Estimated) ICMJE	2024-04-30
Eligibility Criteria ICMJE	Inclusion criteria: • Informed consent has to be obtained from the patient or a legal representative. In case this is not feasible due to the emergency situation, an alternative informed consent procedure is allowed, according to the current legislation in Germany, as described in section 15.4 and 15.5 of this protocol. • Male or female adult, ≥18 to ≤80 years of age. Patients older than 80 years of age may be enrolled after review of an initial safety data set obtained from younger patients as described in section 7.2. • Disabling acute ischemic stroke with an NIHSS score of ≤12 at time of randomization. • Treatment with IMP can be initiated within 24 hours after the onset of stroke or after last known normal. Exclusion criteria: • Patients receiving intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) for the index event (i.e., the current stroke that led to screening the patient for this trial). • Prior inability to walk or to lead an independent life, which is defined as daily need for assistance in performing activities of daily living (ADL). • Patients who are delirious, comatose or stuporous (a score of ≥ 2 on item 1.a of the NIHSS). • Patients undergoing mechanical thrombectomy or intra-arterial thrombolysis. • Detection of hemorrhage on baseline CT. • Severe dysphagia with inability to swallow and no indication for nasogastric tube as per opinion of the investigator and thus inability to administer IMP. • Systolic blood pressure < 110 mmHg at randomization. • Pregnant and breastfeeding patients. Females with childbearing potential must comply with using highly effective methods of contraception as defined in section 9.2. • Reported severe ongoing hepatic impairment (Child Pugh C). • Reported relevant ongoing renal failure with known GFR <30ml/min. • Reported ongoing major depression. • Reported ongoing tracheal obstruction. • Reported ongoing pulmonary hypertension associated with idiopathic interstitial pneumonias (PHIIP) • Reported leucopenia or agranulocytosis. • Reported agranulocytosis during previous treatment with thiourea derivatives. • Reported hypersensitivity to perphenazine or propylthiouracil or riociguat or any of the other excipients. • Participation in another clinical trial within the last four weeks. • Reported use of phosphodiesterase (PDE) inhibitors (such as sildenafil, tadalafil, vardenafil) within the last 7 days. • Reported use of nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs called 'poppers' within the last 7 days. • Reported use of antithyroid drugs within the last 7 days.
Sex/Gender ICMJE	Sexes Eligible for the Study: All
Ages ICMJE	18 Years to 80 Years (Adult, Older Adult)
Accepts Healthy Volunteers ICMJE	No
Location Countries ICMJE	Germany
Removed Location Countries	

Administrative Information

NCT Number ICMJE	NCT05762146
Other Study ID Numbers ICMJE	REPO-STROKE II 2019-000474-31(EudraCT Number)
Has Data Monitoring Committee	Yes
U.S. FDA-regulated Product	Studies a U.S. FDA-regulated Drug Product: No Studies a U.S. FDA-regulated Device Product: No Product manufactured in and exported from the U.S: No
IPD Sharing Statement ICMJE	Plan to Share IPD: No
Current Responsible Party	Maastricht University
Original Responsible Party	Same as current
Current Study Sponsor ICMJE	Maastricht University
Original Study Sponsor ICMJE	Same as current
Collaborators ICMJE	Not provided
Investigators ICMJE	Not provided
PRS Account	Maastricht University

ICMJE Data element required by the International Committee of Medical Journal Editors and the World Health Organization ICTRP