A First-in-Human, randomized, double-blind, placebo-controlled ascending dose study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of STR-324 in healthy subjects.

Published: 18-12-2017
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To investigate the safety, tolerability and efficacy of STR-324 infusions in healthy subjects.Primary objective (Parts 1 and 2)* To assess and characterise the safety and the tolerability of STR-324, over a 4-hour (Part 1) and a 48-h infusion (Part...

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

Summary

ID

NL-OMON46459

Source
ToetsingOnline

Brief title
First-In-Human PainCart study for STR-324

Condition

- Other condition

Synonym
Pain

Health condition

Pain

Research involving
Human

Sponsors and support

Primary sponsor: Stragen France
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: healthy volunteers, pharmacodynamics, pharmacokinetics, veiligheid

Outcome measures

Primary outcome

Tolerability / safety endpoints

Treatment-emergent (serious) adverse events ((S)AEs) will be documented,

regarding incidence, nature and severity from the time the subject signs the

consent until the follow-up visit (End of Study Visit).

The following endpoints will be determined at time points indicated in the

Schedule of Assessments.

* Clinical laboratory tests

o Hematology

o Chemistry

o Coagulation

o Urinalysis

* Vital signs (supine and standing)

o Pulse Rate (bpm)

o Systolic blood pressure (mmHg)

o Diastolic blood pressure (mmHg)

o Respiratory rate

o SpO2

o Temperature

* ECG

o Heart Rate (HR) (bpm), PR, QRS, QT, QTcF.

* Continuous cardiac Holter monitoring (From 30 min before dosing to the end of study drug administration)

o Minimum heart rate

o Maximum heart rate

o Mean Heart rate

o Number of single supraventricular ectopy

o Number of couplets supraventricular ectopy

o Number of single ventricular ectopy

o Number of couplets ventricular ectopy

o Longest RR pauses

o Number of RRs > 2.0 sec

* Urine production (L/24h)

* Angiotensin 2 in plasma (pg/mL)

Secondary outcome

Pharmacokinetic endpoints (plasma and urine)

Pharmacodynamic endpoints Part 1

PainCart

Analogue Scale (VAS) pain Curve (AUC), and post-test VAS.

Opioid effects

* VAS Bond & Lader (Alertness, mood, calmness)

* VAS Bowdle (internal perception, external perception, *feeling high*)

Pharmacodynamic endpoints Part 2

PainCart

* Thermal Pain (Normal Skin): Pain Detection Threshold (PDT).

* Electrical pain Stair and Burst (pre-cold pressor): Pain Tolerance Threshold

(PTT).

* Pressure Pain: Pain Tolerance Threshold (PTT).

* Cold Pressor: Pain Tolerance Threshold (PTT).

* UVB model Thermal pain (Normal skin): Pain Detection Threshold (PDT)

* UVB model Thermal pain (Eerythema skin): Pain Detection Threshold (PDT)

NeuroCart

* Saccadic eye movement

* Smooth pursuit eye movement

* Adaptive tracking

* Body sway

* N-Back

* Pharmaco-EEG: power (resting eyes closed, eyes open condition)

Opioid effects

* Pupillometry (Pupil- and cornea diameter left/right eye)

* VAS Bond & Lader (Alertness, mood, calmness)

* VAS Bowdle (internal perception, external perception, *feeling high*)

* 49-item Addiction Center Research Inventory (ARCI)

* Bowel Function Index [BFI] (Baseline *In last 7 days* and Adapted to *Since start of treatment*)

Enzyme activity

* Aminopeptidase N (APN) (plasma)

* Big Endothelin-1 (Big-ET-1) (plasma)

Study description

Background summary

Nociception defines the ability of an organism to detect noxious stimuli (Wall and Melzack, 2000). It involves a neural process and analysis of the external stimuli to avoid dangerous painful situations that may induce physical damage. In healthy humans, this neural process is regulated by endo-morphines including enkephalins, which play a major role in the modulation of pain. However, this natural modulation is of short duration. Enkephalins are synthesized intracellularly by enzymatic processing of the gene-derived precursor preproenkephalin (Penk1). Stored in large synaptic vesicles, enkephalins are released by a Ca2+ dependent exocytosis mechanism. Outside the cells, enkephalins interact with opioid receptors for a short period of time, then their action is disturbed by the concomitant action of two zinc metallopeptidases * NEP and APN * that generate enkephalin inactive metabolites. These two peptidases cleave enkephalins and thus contribute to the modulation of the nociceptive signaling and processing. Increasing the bioavailability of enkephalins by inhibiting APN and NEP is a new therapeutic paradigm in the management of pain. Small chemical molecules have been described that have the capability of inhibiting both peptidases APN and NEP which are called Dual Enkephalinase Inhibitors or DENKIs. DENKIs have the advantage of being active only when enkephalins are produced in response to a

pain sensation (Roques et al., 2012).

Study objective

To investigate the safety, tolerability and efficacy of STR-324 infusions in healthy subjects.

Primary objective (Parts 1 and 2)
* To assess and characterise the safety and the tolerability of STR-324, over a 4-hour (Part 1) and a 48-h infusion (Part 2).

Secondary objectives (Parts 1 and 2)
* To characterise the pharmacokinetics (PK) in plasma and urine of STR-324 and its main metabolite.
* To characterise the pharmacodynamics (PD) of STR-324 using a battery of evoked pain tasks.
* To examine the pharmacokinetics/pharmacodynamics relationship of any observed efficacy of STR-324 at any of the measured time points.
* To explore any off-target opioid effects of STR-324, including standard cognitive tests (part 1 and part 2) and scotopic pupil diameter (Part 2 only).

Study design

This is an interventional, first-in-man drug study (phase I), double-blind, placebo-controlled, two-part, ascending dose study in healthy volunteers.

Part 1
Part 1 of the study will be conducted as a partial crossover following an interleaving dosing schedule in 30 healthy male volunteers. A total of eight dose levels infused over a period of 4 hours will be investigated in two groups of subjects. Each group consists of 15 subjects that are randomized in a 12:3 ratio (active vs. placebo). Between each group an interim analysis of safety is performed.

Part 2
Part 2 of the study will be conducted as a parallel study in 48 healthy male subjects divided in three groups of 16 subjects Three dose levels will be selected based on the tolerability and estimated efficacy in part 1 for a 48 hour i.v. infusion. Subjects will be randomized in 12:4 (active vs. placebo) fashion.

For both parts, the first administrations (Group 1 and Group 3) will be dosed using a sentinel approach: the first two subjects will be randomized to receive 1 placebo and 1 active and dosed with a 24 hour observation period prior to dosing the remaining subjects of the dose level.

Intervention

Investigational drug
4-hour (part 1) and 48-hour (part 2) continuous i.v. infusion of STR-324 or placebo. In part 1, a total of 8 dose levels will be administered in 40 mL during a 4-hour infusion. Part 2 will be a 48-hour infusion of 480 mL.

Comparative drug
Intravenous saline (NaCl 0.9%) will be used as placebo.

Study burden and risks

The risks associated with the administration of STR-324 to humans have not yet been identified, since this will be the first administration in humans. All study drug administrations will be performed in the clinic under medical supervision. The proposed FIM study consists in a single dose administration, with close monitoring of volunteers* vital functions during and in the 26h following administration. The monitoring of vital function includes the monitoring of respiratory rate, ECG, pupil size (part 2) blood pressure and heart rate. Thus, the subjects will be closely monitored for any adverse signs during the different treatments. Therefore careful observation and medical management will minimize any associated risk in this study. For both study parts, the first administrations will be dosed using a sentinel approach: the first two subjects will be randomized to receive 1 placebo and 1 active and dosed with a 24 hour observation period prior to dosing the remaining subjects of the dose level. For ensuring immediate management of opioid-like toxicities, naloxone, as a specific antidote for substances bound to *- (and to a lesser extent *- and *-) receptors, will be available on site.

Contacts

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Scientific
Stragen France

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed informed consent prior to any study-mandated procedure
2. Healthy male subjects, 18 to 45 years of age, inclusive at screening.
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
4. All males must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
5. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator [(following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature), 12-lead electrocardiogram (ECG)]. Minor deviations of laboratory values from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel, coagulation and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
3. Abnormal renal function (eGFR (MDRD) < 60 v
4. Previous history of seizures or epilepsy.
5. Acute disease state (e.g. nausea, vomiting, fever, or diarrhea) within 7 days before the first study day.

6. Positive Hepatitis B surface antigen (HBsAg), Hepatitis B antibodies, Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
7. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg measured in supine position at screening.
8. Abnormal findings in the resting ECG at screening defined as:
- QTcF> 450 or < 300 msec
- Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm)
- Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker
9. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of study drug administration, or less than 5 half-lives (whichever is longer). Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. No exceptions will be made for known analgesics (e.g. paracetamol or ibuprofen)
10. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator.
11. Participation in an investigational drug or device study within 3 months prior to first dosing.
12. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent.
13. Positive test for drugs of abuse at screening or pre-dose.
14. Positive alcohol breath test at screening or pre-dose. Alcohol will not be allowed from at least 24 hours before screening or pre-dose.
15. Smoker of more than 5 cigarettes per day prior to screening or who use tobacco products equivalent to more than 5 cigarettes per day and unable to abstain from smoking whilst in the unit.
16. Is demonstrating excess in xanthine consumption (more than eight cups of coffee or equivalent per day)
17. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
18. Loss or donation of blood over 500 mL within three months prior to screening or intention to donate blood or blood products during the study.
19. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.
20. Any current, clinically significant, known medical condition in particular any existing conditions that would affect sensitivity to cold (such as atherosclerosis, Raynaud*s disease, urticaria, hypothyroidism) or pain (disease that causes pain, hypesthesia, hyperalgesia, allodynia, paraesthesia, neuropathy, etc.);
21. Subjects indicating pain tests intolerable at screening or achieving tolerance at >80% of maximum input intensity for any pain test for cold, pressure and electrical tests;;Additional exclusion criteria (Part 2 (groups 4 and 5))
22. History or presence of post-inflammatory hyperpigmentation;
23. Dark skin (Fitzpatrick skin type IV, V or VI), widespread acne, freckles, tattoos or scarring

on the back;
24. A MED higher than 355 mJ/cm2 at screening.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-02-2018
Enrollment:	78
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	STR-324
Generic name:	n/a

Ethics review

Approved WMO

Date:	18-12-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	09-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-10-2018
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	EUCTR2014-002402-21-NL
CCMO	NL63085.056.17

Study results

Date completed:	07-11-2018
Results posted:	12-11-2019

First publication
16-10-2019