A proof of concept randomized, double-blind, parallel group, controlled dose-finding and safety study of STR-324 in post-operative pain

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

Summary

ID

NL-OMON54385

Source
ToetsingOnline

Brief title
Dose finding study of STR-324

Condition

- Other condition

Synonym
pain after surgery

Health condition

(postoperatieve) pijn

Research involving

Human

Sponsors and support

Primary sponsor: ALAXIA SAS
Source(s) of monetary or material Support: ALAXIA SAS

Intervention

Keyword: analgesic, postoperative pain, STR-324

Outcome measures

Primary outcome

8.1.1 Primary endpoint

Pain Intensity will be assessed by a Numerical Rating Scale (NRS) before and

during analgesic infusion.

Change of Pain Intensity assessed by the Numerical Rating Scale (NRS) after

initiation of the post-op analgesia and before switch to standard treatment.

Two parameters will be assessed:

Qualitative: a decrease of 2 units minimum from baseline and/or achievement of

a pain score <=3 is considered successful, responder=Yes.

Quantitative: maximum value of the pain score difference versus baseline.

Secondary outcome

8.1.2.1 Efficacy secondary end points

AUC of Pain Intensity assessed by the Numerical Rating Scale (NRS) (11-

points scale) during infusion corrected from baseline

Time to first achieve effect, and in particular maximum effect

Pain level at the end of each infusion level

Percent of responders in each group

Time to switch to standard pain management

Total dose of STR-324

Total dose of morphine HCl (for Step 2 only) before the switch to standard of

care

Comparison of curve profiles

8.1.2.2 Safety end points

Adverse event collection

Haematology parameters

Biochemistry including liver function tests parameters

Vital signs: blood pressure and heart rate, respiratory rate

ECG parameters

Study description

Background summary

STR-324 is a enkephalinase inhibitor that has shown strong analgesic activity in animals. A Phase I study in humans demonstrated that STR-324 was well-tolerated and had a favourable safety and tolerability profile in healthy subjects. We now propose a study in postoperative pain to assess the analgesic effect of STR-324, as compared to standard clinical care using morphine HCl as postoperative analgesic.

Study objective

The main objective of this dose-finding study is to evaluate the analgesic effect of STR-324 (maximum 4 increasing doses and maximum 2-hours infusion) on post-operative pain, measured by change of pain intensity assessed on a Numerical Rating Scale (NRS) using an 11-point scale (0-10).

Study design

This study involves two separate steps:
The first step (single-blind standard group), involving a total of 12 patients, aims to verify the sensitivity of the study setup in the proposed surgery to confirm the validity of the surgery according to the pain and enrolment rate using the established standard treatment (i.e. morphine).
After the first step, data collected on the primary endpoint will be reviewed in order to confirm the sensitivity of this specific pain model. If the sensitivity is not confirmed after step 1, the study will be stopped and study design will be reviewed.
The second step (dose-finding study) is a randomized, double-blind, parallel groups, controlled clinical trial involving a total of 106 patients divided into two groups in which patients will be randomized between STR-324 and morphine HCl in a ratio of 3/1:
Group 1 (n= 53 - 40 verum / 13 morphine HCl): Titration initiated with a 4-mL bolus of the solution
Group 2 (n= 53 - 40 verum / 13 morphine HCl): Titration without initial bolus

Group 1 and 2 will be allocated randomly. Primary analysis of step 2 will be performed as an intention to treat analysis.

Intervention

see study design and relevant pages in the research protocol.

5.1.1 Step 1: Standard group
Morphine HCl will be administered by intermittent boluses:
Total dose administered and stopping criteria will be based on site practice.
5.1.2 Step 2: Test group
Depending on the randomization, the titration will be initiated with a 4-mL (corresponding to 1 mg of STR-324) bolus of the solution (Group 1) or without initial bolus (Group 2). The STR-324 and morphine HCl titration protocol is based on continuous infusion with increasing
rates will be tested (5, 10, 20 and 40 mL/h):
Dose 1: 5 mL/h infusion rate (corresponding to 1.3 mg/h of STR-324 or morphine HCl)
Dose 2: 10 mL/h infusion rate (corresponding to 2.6 mg/h of STR-324 or morphine HCl)
Dose 3: 20 mL/h infusion rate (corresponding to 5.1 mg/h of STR-324 or morphine HCl)
Dose 4: 40 mL/h infusion rate (corresponding to 10.2 mg/h of STR-324 or morphine HCl)
Study drug administration description:
Titration: continuous infusion with increasing infusion rates every 5 minutes until after titration, if pain score is still > 3 at highest dose level: the

study drug will be interrupted and the patient is switched to standard pain management according to the site practice this dose level up to 2 hours.
If during the 2h period score re-increases over 3:
The maximum dose level of study product was not achieved (i.e. maximum infusion rate):
Re-escalation of infusion rate every 5 min based on pain score up to the highest dose level
Pain score > 3 at highest dose level after re-escalation: Switch to standard pain management.
After 2 hours, all patients will be switched to standard pain management.
The exposure to study drug will be lasting from 20 min (maximal titration time up to the highest dose) to a maximum of 2 hours.
Of note, aggravation of the sedation score up to S3 as well as agitation or delirium episodes occurring during or after the study drug administration shall be reported as adverse events.

Study burden and risks

This study aims to evaluate the analgesic effect and the safety of STR-324 administered as an infusion, with or without initial bolus, to patients suffering from post-operative pain. The protocol is based on an initial dose of 1.3 mg/h infusion rate with periodic re-evaluation of the pain and, in case of no response, the possibility of gradually increasing the dose up to the maximum dose (10.2 mg/h).

During this phase IIa clinical trial, the maximal dose is set at 10.2 mg/h and such maximal dose will be achieved after several titration steps. However, a specific attention will be brought to any adverse event, and particularly to the potential effects that could result from the pharmacologic properties of STR-324.

The potential benefit from STR-324 administration consists of analgesia without opioid-like side effects.

Treatment of non-responder patients at the highest dose will be discontinued and replaced with the site standard pain management treatment. Patients responding to the study drug will be followed for a period of two hours and then systematically switched to the site standard pain management treatment.

The exposure to study product will last at least 20 minutes (time required to reach the maximum infusion rate) and at most 2 hours. The duration of morphine treatment will follow the same schedule and therefore cannot exceed 2 hours.

The proposed pain model is similar with the usual post-operative pain management practice; however, the authorized concomitant analgesic medications differ from the usual practice. In this context, in order to confirm the sensitivity of the pain model used in the trial prior to conducting the study,

a standard group of patients treated with morphine is planned to be enrolled in the proposed surgery (Aubrun et al., 2003; Sitbon et al., 2016).

Sponsor considers that the previous data collected in animals and humans, the rationale and the design of this study are in favour of a positive benefit/risk balance for the patients who will participate.

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

1. Patient aged 18-75 years old, at screening;
2. Having signed an informed consent prior to any study-related procedure;
3. Patients planned to undergo a major laparoscopic abdominal or pelvic surgery;
4. Surgery to be performed without local or regional anaesthesia nor

infiltration;
5. Body mass index (BMI) between 18 and 35 kg/m² inclusive at screening;
6. Women of childbearing potential must agree to use at least one effective contraceptive method upon enrolment and for 1 cycle following the last dose of the investigational product.

Exclusion criteria

1. Patient contra-indicated for morphine administration;
2. Unstable or poorly controlled psychiatric condition (e.g., untreated PTSD, major anxiety, or depression). Subjects who take stable doses (same dose >30 days) of antidepressants and/or anti-anxiety drugs may be included;
3. Women who are pregnant or breastfeeding;
4. History of alcohol, opiate or other drug abuse. For alcohol abuse, this means problematic use or >21 standardized alcohol units per week;
5. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment might interfere with the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (according to medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate), 12-lead electrocardiogram (ECG)). Minor deviations of values from the normal range may be accepted, if judged by the Investigator to have no clinical relevance;
6. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel);
7. Participation in an investigational drug or device study within 1 month prior to dosing.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-02-2021
Enrollment:	118
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Morphine
Generic name:	morphine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	STR-324
Generic name:	STR-324

Ethics review

Approved WMO

Date:	13-07-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	16-09-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	01-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	08-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	12-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-10-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-04-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	17-10-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2019-003019-80-NL
ClinicalTrials.gov	NCT04582786
CCMO	NL74239.058.20