A multi-country, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of STA363 at two concentrations (60 mg/mL and 120 mg/mL) compared to placebo in patients with chronic discogenic low back pain

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The primary objective is to investigate the efficacy of a single intradiscal injection of STA363 into one or two IVDs as compared to placebo by the following primary efficacy endpoint:* Change from baseline at Month 6 in mean pain intensity measured...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON49183

Source
ToetsingOnline

Brief title
STA-02

Condition

- Joint disorders

Synonym
chronic discogenic low back pain, low back pain

Research involving
Human

Sponsors and support

Primary sponsor: Stayble Therapeutics
Source(s) of monetary or material Support: Stayble Therapeutics

Intervention

Keyword: back pain, double-blind, efficacy, safety

Outcome measures

Primary outcome

The primary objective is to investigate the efficacy of a single intradiscal

injection of STA363 into one or two IVDs as compared to placebo by the

following primary efficacy endpoint:

* Change from baseline at Month 6 in mean pain intensity measured on a 0-10

Numerical rating scale (NRS) for 7 consecutive days

Secondary outcome

The secondary objectives are to investigate the efficacy of a single

intradiscal injection of STA363 into one or two IVDs as compared to placebo by

the following secondary efficacy endpoints:

* Change from baseline at Month 1, Month 3 and Month 12 in mean pain intensity

measured on the NRS for 7 consecutive days

* Changes from baseline at Month 1, Month 3, Month 6 and Month 12 using the

following questionnaires:

o Oswestry Disability Index (ODI)

o EQ-5D-5L

* Quantitative changes in nucleus pulposus (NP) water content (reflecting

transformation of NP into connective tissue) at Month 6 and Month 12

(T2-weighted magnetic resonance imaging [MRI] and quantification of T2)

To investigate the safety of intradiscal injection of STA363 compared to

placebo by the following safetyendpoints:

* Incidence and nature of adverse events

* Changes in physical examination findings

* Changes in vital signs (blood pressure and heart rate)

* Changes in 12-lead electrocardiogram (ECG)

* Changes in laboratory tests (hematology, clinical chemistry)

* Pain intensity at the injection site during and 15 minutes after injection

(NRS)

* Changes in IVD height (T2-weighted MRI)

* Other changes in IVD morphology (e.g. frequency of asymptomatic/symptomatic

disc protrusions, Modic changes, high-intensity zone [HIZ] as well as other

radiology findings) (T2-weighted MRI)

Exploratory objectives are to investigate the efficacy of a single intradiscal

injection of STA363 into one or two IVDs compared to placebo by the following

exploratory efficacy endpoints:

* Percentage of patients achieving >=30% reduction in mean NRS pain intensity

score from baseline to Month 6

* Percentage of patients achieving >=50% reduction in mean NRS pain intensity

score from baseline to Month 6

* Percentage of patients achieving >=30% improvement in ODI score

* Percentage of patients with success outcome defined as >=50% improvement in

NRS accompanied by a >=30% improvement in ODI

* Consumption of analgesics

* Return to work

* Time to spinal fusion surgery

* Patient Global Impression of Change (PGIC) at Month 1, Month 3, Month 6,

Month 12 measured by a 7-point Likert Scale

Study description

Background summary

Chronic low back pain (cLBP) is a major health problem and a significant burden to patients as well as society [1]. It is one of the leading causes of work absenteeism and health care-related costs [1]. Despite its high prevalence, there are diagnostic challenges, and, in many patients, the proximate cause of the pain cannot be accurately determined. Nevertheless, it has been estimated that more than a third of the cases of chronic low back pain has a discogenic etiology [2]. Diagnosis is made by clinical presentation and imaging [3], predominantly magnetic resonance imaging (MRI) tomography. Provocative discography has been abandoned by many physicians since the usefulness of discography in predicting the outcome of lumbar fusion surgery is low [4]. Spinal fusion surgery is one therapeutic option for patients suffering from cLBP not responding sufficiently well to physio- and pharmacotherapy. The procedure dates back to 1889 but it is in the past 20 years that there has been a great escalation internationally in its use. However, as for all types of surgery, there is a risk for complications and a considerable rehabilitation period. There are several indications for spinal fusion surgery with degenerative disc disease representing 7% of the cases in Sweden in 2014 according to the Swedish Spine Registry [5]. The efficacy of spinal fusion surgery in degenerative disc disease is limited and approximately one third of the patients report no improvement or even worsening of pain one year after the intervention [5]. In 5-year follow-up surveys, similar results have been obtained [5]. Martin et al. examined the USA National Inpatient Sample database from 2004 to 2015 and found that the volume of elective lumbar fusion increased by 62.3% (or 32.1% per 100,000 US adults), from 122,679 cases (60.4 per

100,000) in 2004 to 199,140 (79.8 per 100,000) in 2015. While increases were observed for all diagnoses during the examined 10-year period, those for disc herniation and disc degeneration declined during the most recent years of the study (2013-2015), perhaps as a result of publications challenging conventional thought for these indications, increased scrutiny from payers, and/or improved documentation reflecting more accurate coding [6]. Harris et al. aimed to summarize
systematic reviews on the effectiveness of lumbar spine fusion for most diagnoses. They found no high quality systematic reviews and the risk of bias of the randomized controlled trials in the reviews was generally high. The available evidence did not support a benefit from spine fusion compared to nonoperative alternatives for back pain associated with degeneration [7]. There is thus a clear medical need for new treatment options for cLBP caused by degenerative disc disease. Alterations in disc morphology can be seen as early as in adolescence [8] and are often referred to as *degenerative* changes. Since age-related changes in disc structure eventually develop in all individuals, the concept of disc degeneration has been challenged, as the term implies a pathological process rather than normal aging. However, in some individuals diagnosed with degenerative disc disease, there is a formation of tears and fissures of annulus fibrosus, the outer shell of the disc. These allow inflammatory molecules known to be produced in the nucleus pulposus (NP) (the gelatinous nucleus of the disc) of the degenerating disc to penetrate into and even leak outside the annulus fibrosus. The discovery that disc degeneration causes tears in the annulus fibrosus has been described by Saifuddin et al. [9], and
MacMillan et al. [10] showed that these fissures can serve as diffusion routes from the NP to extradiscal sites. This has been further evaluated in a rat model in which it was demonstrated that diffusion of NP fluid from an intervertebral disc (IVD) causes pain, whereas a superficial scratch on the surface of the disc with no diffusion, does not [11]. Replacement of the NP with connective tissue is a part of natural aging. Since the NP is highly hydrated, fibrosis or at least desiccation can be seen on T2-weighted MRI as a darkening of the center of the disc [12]. This process frequently follows a course in which discogenic cLBP declines over time [13] which may be a consequence of disappearance of NP and a loss of its capacity to generate proinflammatory molecules. Cells of the NP rely on glycolysis for energy metabolism and therefore, the levels of S-lactic acid in the disc are high [14]. Age-related disc fibrosis may result from many different mechanisms, but it is possible that lactic acid is one mediator. The therapeutic principle developed by Stayble Therapeutics mimics the process of age-related disc fibrosis. A single injection of lactic acid into an IVD has been shown to produce a rapid (<4 weeks) and pronounced transformation of NP into connective tissue in pigs. There may be a double therapeutic benefit from this intervention:
1. Generation and diffusion of proinflammatory and pain-producing molecules from the NP is
prevented.

2. Sclerotization of the disc limits motion and stabilizes the affected spinal segment.
Stayble Therapeutics is developing STA363 ((S)-lactic acid for treatment of cLBP of discogenic origin. The final formulation is prepared by an aseptical reconstitution of STA363 ((S)-lactic acid 150 or 300 mg/mL (6.7 mL), with radiocontrast formulation iohexol (Omnipaque®) 300 mg I/mL (10 mL) and should only be used for injection into intervertebral discs (IVDs). Iohexol is used to confirm correct intradiscal injection using x-ray imaging. The final concentration of (S)-lactic acid is 60 or 120 mg/mL. The concentration of iohexol is kept constant at 388 mg/mL, corresponding to 180 mg I/mL, for both doses of (S)-lactic acid. STA363 ((S)-lactic acid acts by transforming the NP of the IVD into connective tissue. This will prevent diffusion of pain-producing and proinflammatory molecules, produced by the degenerating NP, to spinal nerves. The mechanical properties of the IVD will also change so that the motion segment becomes less flexible and consequently partly mimics the effects of a spinal fusion. The formulation has been used for the first time in a phase Ib study in cLBP patients.

Study objective

The primary objective is to investigate the efficacy of a single intradiscal injection of STA363 into one or two IVDs as compared to placebo by the following primary efficacy endpoint:
* Change from baseline at Month 6 in mean pain intensity measured on a 0-10 Numerical rating scale (NRS) for 7 consecutive days

The secondary objectives are to investigate the efficacy of a single intradiscal injection of STA363 into one or two IVDs as compared to placebo by the following secondary efficacy endpoints:
* Change from baseline at Month 1, Month 3 and Month 12 in mean pain intensity measured on the NRS for 7 consecutive days
* Changes from baseline at Month 1, Month 3, Month 6 and Month 12 using the following questionnaires:
o Oswestry Disability Index (ODI)
o EQ-5D-5L
* Quantitative changes in nucleus pulposus (NP) water content (reflecting transformation of NP into connective tissue) at Month 6 and Month 12 (T2-weighted magnetic resonance imaging [MRI] and quantification of T2)

To investigate the safety of intradiscal injection of STA363 compared to placebo by the following safetyendpoints:
* Incidence and nature of adverse events
* Changes in physical examination findings
* Changes in vital signs (blood pressure and heart rate)
* Changes in 12-lead electrocardiogram (ECG)
* Changes in laboratory tests (hematology, clinical chemistry)
* Pain intensity at the injection site during and 15 minutes after injection

(NRS)
* Changes in IVD height (T2-weighted MRI)
* Other changes in IVD morphology (e.g. frequency of asymptomatic/symptomatic disc protrusions, Modic changes, high-intensity zone [HIZ] as well as other radiology findings) (T2-weighted MRI)

Exploratory objectives are to investigate the efficacy of a single intradiscal injection of STA363 into one or two IVDs compared to placebo by the following exploratory efficacy endpoints:
* Percentage of patients achieving >=30% reduction in mean NRS pain intensity score from baseline to Month 6
* Percentage of patients achieving >=50% reduction in mean NRS pain intensity score from baseline to Month 6
* Percentage of patients achieving >=30% improvement in ODI score
* Percentage of patients with success outcome defined as >=50% improvement in NRS accompanied by a >=30% improvement in ODI
* Consumption of analgesics
* Return to work
* Time to spinal fusion surgery
* Patient Global Impression of Change (PGIC) at Month 1, Month 3, Month 6, Month 12 measured by a 7-point Likert Scale

Study design

This is a phase IIb, prospective, multi-country, multicenter, randomized, double-blind, placebocontrolled, parallel group study to investigate the efficacy, safety and transformation of NP following single intradiscal injection of STA363 (lactic acid) into one or two IVDs compared to placebo for the treatment of discogenic low back pain. This study will be conducted in Russia, Spain and the Netherlands. The primary objective is to demonstrate superiority of STA363 over placebo in reducing low back pain as measured by the NRS. A total of 168 patients will be screened in the study with the aim to recruit 126 patients to be randomly allocated to one of the three treatment groups:
Group 1 - 42 patients will receive STA363 containing 90 mg (60 mg/mL) lactic acid
Group 2 - 42 patients will receive STA363 containing 180 mg (120 mg/mL) lactic acid
Group 3 - 42 patients will receive placebo
The investigational medical product (IMP) will be injected into the center of up to two IVDs. Patients with two discs appropriate for treatment will be treated at both affected levels by two separate injections. Each patient will have 5 visits to study site and 1 telephone call. The patient*s total time in the study will be approximately 61 weeks (~15 months) including an 8-week screening period.

Intervention

Group 1 - 42 patients will receive STA363 containing 90 mg (60 mg/mL) lactic acid
Group 2 - 42 patients will receive STA363 containing 180 mg (120 mg/mL) lactic acid
Group 3 - 42 patients will receive placebo

Study burden and risks

Additional burden for the patient are the 5 additional visits to the hospital which are required for the clinical trial. Also the time of such a visit is higher than usual due to the additional interventions/assessments done during these visits.
Total extra burden consists of:
- questionnaires (2 per visit)
- patient diary (7 days at time of visits)
- ECG (3 times)
- MRI (3 times)
- blood draws (2 times)
- physical exam (5 times)

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. Signed informed consent prior to any study related procedures.
2. Male and female patients >=18 and <=70 years.
3. Chronic discogenic low back pain present for more than 6 months prior to the screening visit.
4. Insufficient response or lack of response to at least 6 months of non-operative treatment (analgesics and/or anti-inflammatory medications [paracetamol, non-steroidal anti-inflammatory agents (NSAIDs), opioids],, physiotherapy, rehabilitation therapy etc.).
5. Patients who meet all the following NRS selection criteria:
a. Presence of >=5 pain NRS assessments (entries) for 7 consecutive days.
b. NRS daily pain scores between 3-9.
c. Not more than two ratings «3».
Note! Patients must be blinded to the above described NRS selection criteria.
6. One or two treatable IVDs of Pfirrmann grade 2 to 3 on MRI at L2/3 to L5/S1 as confirmed by a central reader, AND the following criteria are met:
a. Treatable IVD(s) must be IVD(s) with the highest Pfirrmann grade observed in the patient (e.g. a patient with one IVD of grade 3 and four IVDs of grade 2 is considered eligible only if IVD of grade 3 will be injected).
b. Patients with treatable IVD(s) of grade 2 must have all other lumbar discs rated as grade 1.
c. Not more than two IVDs of grade 3 at any lumbar level.
d. No IVDs of grade 4 or 5 at any lumbar level.
7. Ability to understand the written and verbal information about the study.

Exclusion criteria

1. Treatment with any investigational product within 3 months prior to the screening visit.
2. Patients with more than two painful IVDs.
3. A painful IVD above L2/3 level.
4. Current infection or prior history of spinal infection (e.g., discitis,

septic arthritis, epidural abscess) or an active systemic infection.
5. Previous lumbar spine surgery.
6. Previous disc invasive treatment procedures at the affected level(s) (e.g., intradiscal electrothermal therapy, intradiscal radiofrequency thermocoagulation).
7. Evidence of prior lumbar vertebral body fracture or trauma.
8. Need for spinal decompression assessed by the Investigator.
9. Presence of IVD extrusion or sequestration, or other radiologic findings that in the opinion of the investigator disqualify the patient from being included.
10. Spondylolisthesis or retrolisthesis Grade 2 and above or spondylolysis at the index or adjacent level(s).
11. Lumbar spondylitis or other undifferentiated spondyloarthropathy affecting the index IVD.
12. Patients previously included in the study.
13. Patients suffering from psychosomatic pain in the opinion of the Investigator.
14. Leg pain of compressive origin.
15. Patients requiring continuous treatment with warfarin or other anticoagulant therapy.
16. History of significant neurologic or psychiatric disorders including dementia or seizures.
17. Known alcohol and/or drug abuse.
18. Severe intercurrent illness (e.g. rheumatic disease or chronic pain syndrome) or concomitant treatment (e.g. immunosuppressive drugs), which, in the opinion of the Investigator, may put the patient at risk when participating in the study, or affect the patient*s ability to take part in the study.
19. Pregnant or lactating females, or intention to become pregnant within the study period.
20. Known allergy to any of the components of the drug product or placebo.
21. Known allergy or intolerance to the contrast agent Omnipaque®.
22. Known opioid allergy or intolerance.
23. Any other condition that, in the opinion of the Investigator, precludes the patient from taking part in
this study.
24. Any specific contraindication for MRI such as claustrophobia, intracranial clips or pacemakers.

Study design

Design

Study phase: 2

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):	11-08-2020
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	placebo
Generic name:	water for injection mixed with radiocontrast formulation iohexol
Product type:	Medicine
Brand name:	STA363
Generic name:	(S)-lactic acid

Ethics review

Approved WMO Date:	17-03-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-06-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-08-2020

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2019-004943-54-NL
CCMO	NL73010.091.20

Study results