A 2-stage study to evaluate single doses of MZ-004 at different dose levels in patients with chronic total occlusions. STAGE 1: Open label Training Stage. STAGE 2: Double-blind, randomized, Placebo-Controlled Stage. The TOSCA-5 Study (Total Occlusion Study in Coronary Arteries-5)

Published: 26-05-2015
Last updated: 13-04-2024

To obtain an estimate of the anterograde PCI success rate for patients with a confirmed target CTO in each treatment group and to explore safety and tolerability in these patients.

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

Summary

ID

NL-OMON41937

Source
ToetsingOnline

Brief title
CTO-201 or TOSCA-5 Study

Condition

- Coronary artery disorders

Synonym

complete occlusion of a coronary artery, coronary chronic total occlusion

Research involving
Human

Sponsors and support

Primary sponsor: Matrizyme Pharma Corp.
Source(s) of monetary or material Support: Matrizyne Pharma Corp.

Intervention

Keyword: Chronic total occlusion, Collagenase, Percutaneous coronary intervention

Outcome measures

Primary outcome

The primary endpoint is to estimate the success percentage of anterograde PCI of the CTO lesion in patients who have been treated with MZ-004 compared to those who are treated with placebo. Additionally, safety and tolerability of the drug will be evaluated.

Secondary outcome

The secondary endpoints are to make a comparison between the successfully treated patients and the non-successfully treated patients within the three treatment options when it comes to:

- Fluoroscopy time

- Total procedure time

- Ability to pass a soft wire through the CTO (True-to-true soft wire pass ability, soft wire passage (2 cm behind the proximal layer of the CTO, either intraluminal or extraluminal)

Study description

Background summary

This trial will be performed in order to investigate whether the new drug *MZ-004* will ensure that a coronary artery which has been occluded for a longer period of time can be treated with PCI. A bloodvessel with no flow is called an occluded vessel, a vessel that is completely occluded for over 3 months is called a *chronic total occlusion* (CTO). Patients will be asked to participate in this trial in case they have a CTO.

Some patients who are suffering from a CTO experience severe symptoms such as angina and/or shortness of breath (during exercise). Patients with severe impaired blood flow through their coronary arteries usually have to undergo a medical procedure which is called *percutaneous coronary intervention* (PCI). This treatment is not an operation, it is a procedure which is being performed through the radial or femoral artery and where the coronary artery is being opened and, if possible, a stent is placed.
However, a CTO can be very hard to treat as it usually is a difficult occlusion to penetrate. In most cases this is caused by a cap of collagen at the proximal end of the CTO, which in 40-50% of cases cannot be penetrated with a wire. In that case, the only treatment options left to try to relieve the complaints of the patient are with medication or with surgery called Coronary Artery Bypass Grafting (CABG). In the past few years a drug has been developed, MZ-004, in order to make the proximal end of the CTO more accessible for treatment. MZ-004 is a collagenase that is able to degrade several types of collagen.

In the past, animal studies have been carried out with MZ-004, which showed that MZ-004 is capable of making CTOs more soft in order to advance wires through the CTO lesion more easily. In humans the CTO-1 trial has been carried out, in which MZ-004 has been given to patients who had experienced a failed attempt to open the CTO (28 patients). At the end of this trial, in 75% of the patients the attempt to open the CTO was successfully.

The PCI of CTOs is not experimental, the drug MZ-004 however is experimental.

Study objective

To obtain an estimate of the anterograde PCI success rate for patients with a confirmed target CTO in each treatment group and to explore safety and tolerability in these patients.

Study design

This trial is a doubleblind placebocontrolled randomized trial. It exists of

two parts: a training stage and the main study. A maximum of two to three patients per site will participate in the training stage and will receive MZ-004, an additional average of ten to fifteen patients per site will be included in the main trial. Several sites in Canada and The Netherlands will participate in the trial.

Intervention

During this investigation, the *study drug* (MZ-004 or placebo) will be injected in the occluded coronary artery just proximal to the CTO or in the CTO, using a microcatheter that is being positioned using coronary artery grafting with a contrast medium and X-ray imaging. The injection time is approximately twelve to 17 minutes.

Study burden and risks

Patient burden

The patients participating in the trial will have to endure the highest burden at the start of the enrollment, because of the 3 day hospital admission. During this admission several, relatively easy to endure, tests will be performed such as venapunction, ECGs and echocardiographies. These tests are standard, as they are being performed in order to ensure patient safety and to learn more about the pharmacokinetic properties and side effects of the investigational drug. After the index procedure, the follow-up is pretty standard and does not carry, to our knowledge, a very high burden for the patients. They do, however, need to come to the AMC for the additional testing.

Furthermore, in case of uncertainty whether patients are angiographically eligible to participate in this trial or not, an additional coronary angiography will have to be performed with the concomitant burden and risks. This procedure could be necessary to perform in order to be able to assess whether the trial can be carried out in the most safe way or not. We, however, expect that in most cases we do not need to perform this extra angiography procedure.

Furthermore, some patients participating in this trial will be prone to a higher psychological burden, mainly because they have already experienced a failed attempt to open their CTO and participation in this trial can raise high expectations which are possibly not met. We are, ofcourse, aware of this dilemma, but we believe that the possible benefits of this trial in the long run outweigh the temporary negative aspect of creating false hope.

Risks
The usual risks of venapunction, echocardiography, ECGs, angiography, PCI and

the usage of stents apply in this trial. These risks are not different for the tests carried out in the setting of this trial.

MZ-004
This is the second trial administering MZ-004 to people. The previous trial, called CTO-1, has been completed. 28 patients completed the trial. In total, 114 side-effects were reported by the patients. 7 side-effects were seen as possibly or in some distant manner related to MZ-004 (e.g. low blood pressure, chest pain, rise in cardiac biomarkers, a fall in thrombocyte count, fever, pericardial effusion post angioplasty and nausea). The other 107 side-effects were related to the angioplasty, or were of another origin. 102 of these side-effects were considered to be mild, 12 were considered to be severe (1 repeat angiography post-PCI because the patient had persistent angina, 1 report of low blood pressure, 2 reports of a rise in cardiac enzymes, 2 reports of vasovagal episodes consisting of some dizziness and loss of consciousness, 1 report of hemorrhage at the entry point of the catheter, 1 perforation of the artery during a repeat angiography months after the index procedure resulting in pericardial effusion, 1 case of chest pain, 1 report of arm pain and 1 case of pulmonary carcinoma discovered during the 3 month follow-up visit. This case of cancer was considered not to be related to MZ-004. Except for the pulmonary cancer, all side-effects resolved over time

An additional side-effect that was monitored during the animal studies was the development of a mild to moderate hemorrhage in the myocardial tissue post MZ-004 infusion. The myocardial hemorrhage resolved without intervention.

Placebo
Some patients will receive placebo treatment, which could be considered as treating the CTO in a standard way, which could lead to persistence of complaints of chest pain and shortness of breath.

Unforeseeable risks
It is possible that some patients will experience risks/side-effects that are not mentioned above. As the treatment with MZ-004 is experimental, there is a possibility that risks/side-effects will arise during the trial which could not be foreseen. These side-effects could be mild and dissolve within time without any intervention. However, the possibility exists that severe side-effects will occur leading to persistent impairment or even death.

Risks for a embryo or fetus
The administration of MZ-004 could enhance unknown risks for a embryo or fetus. Because of this lack of knowledge, patients who are pregnant or could be pregnant cannot participate in the trial.

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

A patient will be eligible for the study if s/he meets all of the following criteria:
1. Patient has provided signed and dated informed consent in accordance with required regulations.
2. Patient is male or female * 18 years of age.
3. If patient is a female of childbearing potential, patient is willing to utilize contraception from Screening through the duration of the study. Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to Screening), intra-uterine device (IUD), Depo-Provera®, Norplant® System Implants, surgical sterilization (bilateral tubal ligation, hysterectomy, partner vasectomy), condom or diaphragm or cervical cap plus either contraceptive sponge, foam or jelly. For the purpose of this Study, women of non-childbearing potential are:
a. Females, regardless of age, with functioning ovaries who have a current documented tubal

ligation, or who are surgically sterile (i.e. documented total hysterectomy or bilateral oophorectomy) or
b. Females > 45 years of age who are post-menopausal for greater than 1 year (i.e. last menstrual period > 1 year) at Screening.
4. Patient is willing and able to comply with the protocol requirements during the study and be willing to refrain from any other elective cardiac revascularization procedures for the duration of study participation, unless medically necessary.
5. The patient has a clinically driven, planned PCI of the target CTO, in a major epicardial coronary artery, without planned revascularization of other coronary stenosis/stenoses in major epicardial segments.
6. Target CTO must be * 3 calendar months old by either:
a. Proven Chronicity: Angiographic documentation (conventional or coronary) of the target CTO 3 or more calendar months prior to Screening or
b. Assumed Chronicity: Identification of the target occlusion has occurred in the setting of chronic ischemic heart disease, with no known or suspected acute coronary syndrome (ACS) within 3 months.
7. The patient is receiving a course of optimal anti-ischemic medical therapy (at least 2 anti-anginal agents or the maximum tolerated anti-anginal therapy). Medical therapy should include adequate ventricular rate-limiting medication (i.e. Beta-blocker or calcium antagonist) where appropriate.
*
8. For Stream 1 patients only: The patient has a previous failed PCI, with documentation available to the Investigator and Sponsor, confirming that the failed PCI attempt on the target CTO meets the following criteria:
a. Using anterograde techniques, the operator used at least one Category A guide wire and at least one Category B guide wire during the failed PCI attempt and
b. The operator was unable to establish continuity between the proximal and distal true lumen by advancing any guide wire across the target CTO and
c. The overall fluoroscopy time for the entire procedure during the failed PCI attempt was > 15 minutes.
Category A wires are enhanced tip-load (* 2.5 g) specialized coronary guide wires including Miracle Bros, any Confianza, any Conquest, Abbott Vascular Pilot 150, 200, any Progress, any Cross-it XT, Gaia Second, Gaia Third. Commercially available wires, not listed here, that meet Category A requirements may be permitted upon Sponsor approval.
Category B wires are soft-tip, polymer-jacketed coronary guide wires including Fielder XT, Fielder FC, Pilot 50, Sion Black, Shinobi. Commercially available wires, not listed here, that meet Category B requirements may be permitted upon Sponsor approval.
Patients with a prior PCI failure meeting all above criteria, EXCEPT a Category B guide wire was not used in the failed attempt, are considered Modified Stream 1 patients. Before randomization on Day 0, Modified Stream 1 patients will undergo a Qualifying PCI using a Category B wire.
If the inverse is true and a Category B wire was used but not a Category A wire, the patient will be a Modified Stream 1 and the operator will use a Category A wire during the Qualifying PCI.
9. The patient*s Risk Criteria has been classified AND
a. The site has specified the most relevant functional test performed within the last 6 months (if > 1) used to classify risk OR the Investigator has provided a clear explanation as to why a

functional test has not been performed (written in the patient*s files (i.e. *ETT +ve at 6 minutes 8 months ago, then failed CTO attempt, no events, now referred for trial.*) AND b. The hard copy results of the functional test used to classify risk are available in the patient*s files OR the Investigator has employed the variables used in the risk criteria to describe the result of the most relevant functional test, even if that test was performed elsewhere.

Exclusion criteria

A patient who meets any of the following criteria will not be eligible for the study:;1.Patient has documented chest radiation exposure > 4.0 Gray within 8 weeks of Day 0 (not including any Day 0 procedures). In the absence of Gray dosimetry, patients with > 60 minutes fluoroscopy time within 8 weeks of Day 0 will be excluded. ;2.Patient*s target vessel is a saphenous vein graft occlusion.;3.Patient*s target lesion includes an occluded coronary stent.;4.Patient had ACS < 4 weeks from Screening, attributable to any coronary vessel. ;5.Patient had ACS from 4 weeks to 3 calendar months prior to Screening, attributable to the target CTO. NOTE: If ACS is attributable to a different CTO the patient may still qualify. ;6.Patient has known sensitivity to collagenase.;7.Patient has prior injected collagenase and/or any intra-coronary administration of collagenase.;8.Patient was treated in study CTO-1.;9.Patient has a known sensitivity to contrast dye.;10.Patient has estimated glomerular filtration rate (GFR) is < 30 mL/min, as provided for in the clinical chemistry results available at/for Screening.;11.Patient has any medical condition, which in the judgment of the Investigator and/or Sponsor makes the patient a poor candidate for the investigational procedure.;12.Patient is a pregnant or lactating female (check at Screening and Day 0 before randomization).;13.Patient used any investigational or experimental drug or device within 30 days of Screening.

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):	20-10-2015
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MZ-004
Generic name:	MZ-004

Ethics review

Approved WMO Date:	26-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-004649-28-NL
ClinicalTrials.gov	NCT01753180
CCMO	NL51843.018.15