Part I : Trial related part of the protocol

1 Title of the trial

Local injection of collagenase clostridium histolyticum (Xiapex^{R}) for refractory gastrointestinal strictures: an open-label pilot study.

2 Trial number

Protocol:AGO/2018/004

EudraCT number: 2018-003637-14

3 Objective of the study

To investigate whether intralaesional injection with collagenase clostridium histolyticum (Xiapex^{R}) into the stricture followed by dilation 24 hours later improves the outcome of patients with refractory gastrointestinal strictures as compared to dilation alone (standard of care).

4 End point(s) and timepoint(s) of evaluation

Primary outcome measure:

Number of repeat dilations that are required over a timespan of 6 months.

Secondary outcome measures:

1) time to first repeat dilation

2) complication rate.

3) For upper gastrointestinal strictures only: Dysphagia/gastric outlet obstruction score (0:, able to eat normal diet; 1: moderate passage: able to eat some solid foods;

2: poor passage: able to eat semi-solid foods only; 3: very poor passage: able to drink liquids only; 4: no oral intake possible

4) For lower gastrointestinal strictures only: (Ileo)colorectal obstruction scoring system (0, requiring continuous decompression; 1, no oral intake; 2, liquid or enteral nutrition; 3, oral intake of soft solids, low-residue diet, or full diet with symptoms of stricture*; and 4, oral intake of soft solids, low-residue diet, or full diet without symptoms of stricture*. Symptoms of stricture include abdominal pain/cramps, abdominal distension, nausea, vomiting, constipation, and diarrhea which are related to gastrointestinal transit).

5 General information

5.1 Investigator(s)

Dr. Pieter Hindryckx

Department of Gastro-Enterology

Ghent University Hospital

Pieter.Hindryckx@uzgent.be (+3293320726)

5.2 Sponsor

Ghent University Hospital, with a grant of the Belgian Society of Gastrointestinal Endoscopy.

5.3 Departments/laboratories involved in the study

Department of Gastro-enterology

Ghent University Hospital,

Corneel Heymanslaan 10

9000 Ghent

6 Introduction

The main causes of benign gastrointestinal (GI) strictures are inflammatory (eg: reflux disease, eosinophilic esophagitis, Crohn's disease, caustic…) or iatrogenic (post-irradiation, post endoscopic (sub)mucosal resection, post radiofrequency ablation, anastomotic…). Most strictures respond well to endoscopic balloon dilation. Nonetheless, more than one third of patients develop recurrent symptoms after dilation within the first year (1).

In some case, the stricture can be difficult to treat and require multiple dilation sessions to obtain long-term relief of dysphagia, eating difficulties or lower GI obstructive symptoms (2, 3). A refractory stricture is defined as a cicatricial or fibrotic narrowing luminal diameter resulting in clinical symptoms of a) dysphagia (esophageal strictures), b) gastric outlet obstruction (for strictures of the stomach, pylorus, duodenum of gastrojejunal anastomosis) or c) lower GI obstruction (abdominal distension and cramps, vomiting) with an inability to successfully remediate the anatomic problem to a sufficient diameter over 3 dilation sessions at two-week intervals (4). A recurrent stricture is defined as a cicatricial or fibrotic narrowing with an inability to maintain a satisfactory luminal diameter for four weeks (4). Several options (stenting, intralesional injection of corticosteroids, needle knife incision) have been proposed to manage these strictures, with a varying success rate (5). A significant proportion of patients will finally need self-bougienage or surgery (5).

In conclusion, the treatment of GI strictures remains a challenge for clinicians and there is an unmet need for novel approaches to manage the patients suffering from this condition in order to avoid repeated dilations and/or invasive surgery.

Xiapex^{R} is a locally injectable collagenase approved for the management of Dupuytren's and Peyronie's disease (6, 7). Xiapex is a mixture of two collagenases, enzymes produced by the bacterium *Clostridium histolyticum* that dismantle collagen. Approximately 24 hours after local injection, the collagen fibres have lost their

strength and can be easily broken by manipulation. This therapy has been a breakthrough in the management of Dupuytren's disease, avoiding surgery in the vast majority of patients (6).
After local injection, the collagenases do not reach the bloodstream in significant amounts and are presumed to largely stay at the point of injection until they are broken down by proteases. As a result, side effects are uncommon and are most often injection site reactions including lymphadenopathy (swollen lymph nodes), itching, pain, oedema, and bleeding (for example in the form of bruises or ecchymoses). Allergic reactions are seen in less than 1% of patients (8).

Xiapex^{R} has been proposed as a promising treatment for refractory urethral strictures but has never been evaluated in refractory GI strictures (9).

7 The present study

7.1 Study design

Proof of concept open pilot study with a historical control cohort.

7.2 Medication

7.2.1 Composition and dosing

One vial (0.9mg) xiapex in 3ml dissolvent (also provided by the company) will be divided over 4 quadrants within the fibrotic stricture

7.2.2 Producer

Lonza AG
Lonzastrasse
3930 Visp
Switzerland

7.2.3 Distributor

Swedish Orphan Biovitrum AB
SE-112 76 Stockholm

Sweden

7.2.4 Packaging

Xiapex powder is supplied in a clear glass vial (3 ml, type I glass) with rubber stopper, aluminium seal and flip-off cap (polypropylene). Solvent: 3 ml solution supplied in a clear glass vial (5 ml, type I glass) with rubber stopper, aluminium seal and flip-off cap (polypropylene).

7.2.5 Administration way

Intralaesional injection.

7.2.6 Labelling

Xiapex is a commercialized product and the commercially available labelling will be used. A study label will be applied to the medication (not obscuring the original label), with following information:

Xiapex 0,9 mg poeder en 3 ml oplosmiddel voor oplossing voor injectie

EudraCT N°: 2018-003637-14

TRIAL subject ID nr: _____ Initialen: _____
Datum/ Date visite: _____

ENKEL VOOR STUDIEGEBRUIK Gebruiksaanwijzing: Eén vial (0.9mg) xiapex in 3 ml oplosmiddel intralaesioneel (verdeeld over 4 kwadranten van fibrotische strictuur). Buiten het zicht en bereik van kinderen houden - Bewaren in de koelkast (2-8°C) in de oorspronkelijke verpakking

Contactpersoon: Prof Dr. Pieter Hindryckx, Tel: 0485638106

Sponsor: UZ Gent, Corneel Heymanslaan 10, 9000 Gent

7.2.7 Storage conditions

Store in a refrigerator (2°C - 8°C).
Do not freeze.

7.2.8 Known side effects of the medication

After local injection the collagenases do not reach the bloodstream in significant amounts and are presumed to largely stay at the point of injection until they are broken down by proteases. As a result, side effects are uncommon and are most often injection site reactions including lymphadenopathy (swollen lymph nodes), itching, pain, oedema, and bleeding (for example in the form of bruises or ecchymoses). Allergic reactions are seen in less than 1% of patients Drug accountability

7.2.9 Drug accountability

Drug accountability will be documented.

7.3 The subjects

7.3.1 Number of subjects

Active group: 10 patients presenting with refractory GI strictures.

Control group: A historical cohort that consists of 40 consecutive patients that received an endoscopic balloon dilation 12-15mm for a refractory GI stricture at our centre.

7.3.2 Inclusion criteria

The patient is 18-90 years old
The patient suffers from a GI stricture
The stricture is amenable for endoscopic dilation
The patient has undergone at least 1 previous endoscopic dilation for the same stricture within the last 3 months
The patient has signed the ICF

7.3.3 Exclusion criteria

The patient is not fluent in Dutch

7.3.4 Replacement of subjects

Patients that are not able to participate to the study will receive the standard of care, consisting of endoscopic dilations alone. Only 1 intralaesional administration of the study drug is given at the start of the experiment. Early drop-out of the study (before 6 months) will therefore not impact further standard care of the patient.

7.3.5 Restrictions and prohibitions for the subjects

- Patient need fasting for at least 8 hours prior to the gastroscopies
- Patients on anticoagulant medication need to interrupt the treatment according to the recommendations of the treating physician (Prof dr. Pieter Hindryckx or prof dr Danny De Looze)

7.3.6 Possible advantages and risks for the subjects

It is possible that participation to the study will result in less need for repeat dilations for a refractory upper GI stricture (unknown).

Every dilation carries the risk of perforation, even in the most experiences hands. No additional dilations are performed in light of the study. It is unknown whether local injection of the study drug augments the risks of perforation.
Every patient is carefully monitored after dilation (standard of care). Upon clinical suspicion of perforation, a CT scan is performed for confirmation. In case of confirmed perforation, endoscopic stenting is immediately performed to bridge the defect, allowing healing of the defect. The stent can most of the time be removed after 6 weeks. In some case, endoscopic clipping is the treatment of choice to close the iatrogenic perforation. Surgical intervention is seldomly needed

Side effects of the study drug (Xiapex^{R}) are expected to be very limited, as the study drug does not enter the bloodstream in significant amounts and is rapidly degraded in the bloodstream by proteases. Local reactions (bleeding, swelling, inflammation) are theoretically possible. Like all foreign substances, Xiapex can induce allergic reactions but these seem to be very rare (only 1 case described in literature).

8 Procedures

8.1 Procedures

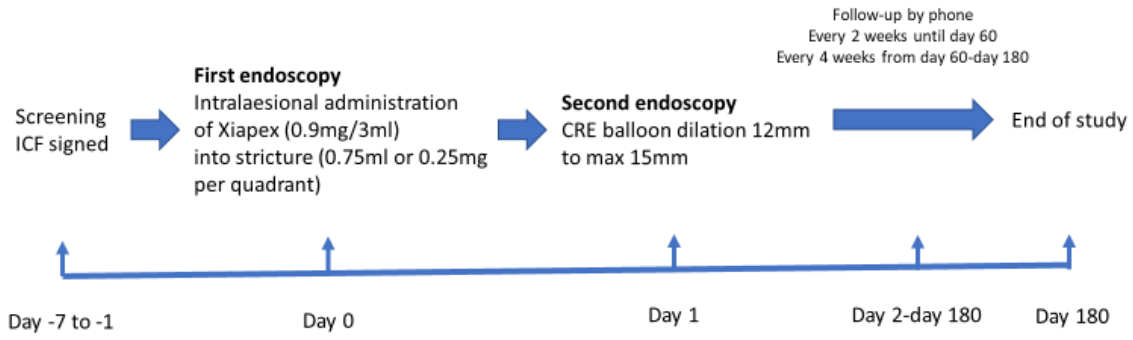
After informed consent, patients with an a refractory upper GI stricture will receive a first esophagogastroscopy or ileocolonoscopy with local injection of Xiapex^{R} injection into the stricture prior to dilatation. One vial (0.9mg) xiapex in 3ml dissolvent (also provided by the company) will be divided over 4 quadrants within the fibrotic stricture. After 24 hours, a second esophagogastroscopy or ileocolonoscopy will be performed to perform balloon dilation of the stricture 12-15mm (standard of care).
The historical cohort will not undergo any procedures, but their patient file will be reviewed to gain outcome data. ICF will be obtained if the patient is still in follow-up at our department.

8.2 Flowchart

- Between day -7 to day -1: Informed consent

- Day 0: Endoscopy, xiapex injection into the strictures (4 quadrants, 0.75ml or 0.25mg per quadrant)
- Day +1: Endoscopy, CRE balloon dilation 12mm to max 15mm
- Day +2 to month 2: clinical evaluation (by phone) every 2 weeks with a window of 3 days (see above for primary and secondary outcome measures)
- Month 2-month 6: Clinical evaluation (by phone) every 4 weeks with a window of 3 days (see above for primary and secondary outcome measures)

The expected total duration of the trial is 18 months.



9 Randomisation / blinding

Not Applicable, as this is an open label trial.

10 Prior and concomitant therapy

Patients on anticoagulant medication need to interrupt the treatment according to the recommendations of the treating physician (Prof dr. Pieter Hindryckx or prof dr Danny De Looze).
All other prior or concomitant medications are allowed

11 Adverse event reporting

List of abbreviations

AE	Adverse Event
CA	Competent Authority
EC	Ethics Committee
SAE	Serious Adverse Event
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

Adverse events (AE)

The following information will be recorded:

- nature of adverse event
- date and time of occurrence and disappearance
- intensity: mild, moderate or severe
- frequency: once, continuous or intermittent
- decision regarding study: continuation or withdrawal
- relation to the study medication (see below)

AE's will be recorded from the first drug administration until the end of the trial. Special attention will be given to those subjects who have discontinued the trial for an AE, or who experienced a severe or a serious AE.

Definitions of Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Avent (SAE)

Any untoward medical occurrence that at any dose:
- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or
- is a congenital anomaly/birth defect.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

Unexpected adverse event

An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Life-threatening
Any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Associated with the use of the drug
An adverse event is considered associated with the use of the drug if the attribution is possible, probable or definitive.

Attribution definitions

Not related
An adverse event which is not related to the use of the drug.

Unlikely
An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s), concomitant disease(s), - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

Probable
An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s), concomitant disease(s).

Definitely
An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

Reporting of adverse events

Adverse events will be reported between the first dose administration of trial medication and the last trial related activity.
All AEs and SAE's will be recorded in the patient's file and in the CRF. All SAE's will be reported as described below.
Medical events that occur between signing of the Informed Consent and the first intake of trial medication will be documented on the medical and surgical history section and concomitant diseases page of the CRF.
SAE's occurring within a period of 30 days following the last intake of trial medication will also be handled as such if spontaneously reported to the investigator.

All serious adverse events (SAE) and pregnancies occurring during clinical trials must be reported by the Principal Investigator within 2 working days after becoming aware of the SAE to:

- HIRUZ of the University Hospital Ghent. HIRUZ will submit the finalized report to the Central Ethics Committee.

This reporting is done by using the appropriate SAE form. For the contact details, see below.

It is the responsibility of the local Principal Investigator to report the local SAE's to the local EC.

In case the investigator decides the SAE is a SUSAR (Suspected Unexpected Serious Adverse Reaction), HIRUZ will report the SUSAR to the Central EC and the CA within the timelines as defined in national legislation. The National Coordinating Investigator reports the SUSAR to all local Principal Investigators.

In case of a life-threatening SUSAR the entire reporting process must be completed within 7 calendar days. In case of a non life-threatening SUSAR the reporting process must completed within 15 calendar days.

The first report of a serious adverse event may be made by telephone, e-mail or facsimile (FAX).

Contact details of the Health, innovation and research institute (HIRUZ):
e-mail: hiruz.ctu@uzgent.be
tel.: 09/332 05 00
fax: 09/332 05 20

Contact details of the Principal Investigator:
e-mail: Pieter.hindryckx@uzgent.be
tel.: In hospital: 093320726; cellphone 0485638106
fax: 093324984

The investigator must provide the minimal information: i.e. trial number, subject's initials and date of birth, medication code number, period of intake, nature of the adverse event and investigator's attribution.
This report of a serious adverse event by telephone must always be confirmed by a written, more detailed report. For this purpose the appropriate SAE form will be used.
Pregnancies occurring during clinical trials are considered immediately reportable events. They must be reported as soon as possible using the same SAE form. The outcome of the pregnancy must also be reported.

All subjects will receive a "trial card" indicating the name of the investigational product, the trial number, the investigator's name and a 24-hour emergency contact number.

12 Study analysis

12.1 Sample size calculation

No sample size calculation, proof of concept open label study.

12.2 Analysis of the samples

Not applicable (no sample taking)

12.3 Statistical analysis

This is a proof of concept open label study that will compare outcome data with a historical control group. Only descriptive analyses will be performed, the sample size will be too low for any meaningful statistical analysis.

13 Quality control and quality assurance

The principal investigator will prospectively collect the pseudonymized data and ensure the quality of the study procedures and study data (see also section 17 up to 21).

14 Indemnity insurance

A No Fault Insurance (of the Ghent University Hospital) will be provided for this trial.

15 Publication policy

All data are owned by the principal investigator (Prof Dr. Pieter Hindryckx) who will set up the author list and author ranking of any abstract or manuscript with regard to the study.

Part II : General part of the protocol

16 Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

This trial can only be undertaken after full approval of the protocol and addenda has been obtained from the IEC/IRB. This document must be dated and clearly identify the protocol, amendments (if any), the informed consent form and any applicable recruiting materials and subject compensation programs approved.
During the trial, the following documents will be sent to the IEC/IRB for their review:

- reports of adverse events as described in section 11.
- all protocol amendments and revised informed consent form (if any).

Amendments should not be implemented without prior review and documented approval / favorable opinion form the IEC/IRB except when necessary to eliminate an immediate hazard to trial subjects or when the change involves only logistical or administrative aspects of the trial.
Reports on, and reviews of the trial and its progress will be submitted to the IEC/IRB by the investigator at intervals stipulated in their guidelines.
At the end of the trial, the investigator will notify the IEC/IRB about the trial completion.

17 ICH/GCP guidelines

This trial will be conducted in accordance with the protocol, current ICH-GCP guidelines and applicable law(s).
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

18 Subject information and informed consent

Prior to entry in the trial, the investigator must explain to potential subjects or their legal representatives the trial and the implication of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorized persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access.

After this explanation and before entry to the trial, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.
The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.
In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent.
Subjects who are unable to comprehend the information provided or pediatric subjects can only be enrolled after consent of a legally acceptable representative.

19 Case Report Forms

The source documents are to be completed at the time of the subject's visit. The CRFs are to be completed within reasonable time after the subject's visit.
The investigator must verify that all data entries in the CRFs are accurate and correct. If certain information is Not Done, Not Available or Not Applicable, the investigator must enter "N.D." or "N.AV." or "N.AP", respectively in the appropriate space.

20 Direct access to source data / documents

The investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

21 Data handling and record keeping

The investigator and sponsor specific essential documents will be retained for at least 20 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirement(s).

22 Signature page

Investigator:

Name: _____

Title: _____

Signature: _____

Date: _____

Investigator:

Name: _____

Title: _____

Signature: _____

Date: _____

References:

1: Said A, Brust DJ, Gaumnitz EA, et al. Predictors of early recurrence of benign esophageal strictures. Am J Gastroenterol. 2003;98:1252-6.

2: Mendelson AH, Small AJ, Agarwalla A, et al. BS Benign anastomotic strictures after esophagectomy: long-term effectiveness of balloon dilation and factors affecting recurrence in 155 patients. Clin Gastroenterol Hepatol. 2015;13:263–71.

3: Pereira-Lima JC, Ramieres RP, Zamin I, Jr, et al. Endoscopic dilation of benign esophageal strictures: report on 1043 procedures. Am J Gastroenterol. 1999;94:1497–1501.

4: Kochman ML, McClave SA, Boyce HW. The refractory and the recurrent esophageal stricture: a definition. Gastrointest Endosc. 2005;62:474–5.

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8: Peimer CA, Wilbrand S, Gerber RA, et al. Safety and tolerability of collagenase Clostridium histolyticum and fasciectomy for Dupuytren's contracture. J Hand Surg Eur Vol. 2015;40:141-9.

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