Title Page

Protocol Title: A randomized double-blind, double dummy, active comparator-controlled dose-finding study in patients with erosive esophagitis due to gastro-esophageal reflux disease (GERD) Los Angeles grade C or D, and patients with at least partial symptom response but endoscopically still unhealed after 8 weeks history of standard treatment healing course with proton-pump inhibitor (PPI), to investigate safety, tolerability, and healing rates after 4 weeks treatment of X842 or lansoprazole, and symptom pattern during subsequent 4 weeks treatment with lansoprazole

Protocol Number: CX842A2201

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Version Number: 3.0

Compound Number: X842

Sponsor Name and Legal Registered Address: Cinclus Pharma AG
Gartenstrasse 101,
CH-4002 Basel, Switzerland

Regulatory Agency Identifying Number(s):

European Clinical Trials Database (EudraCT No.): 2020-003319-91

Approval Date: 25 February 2022

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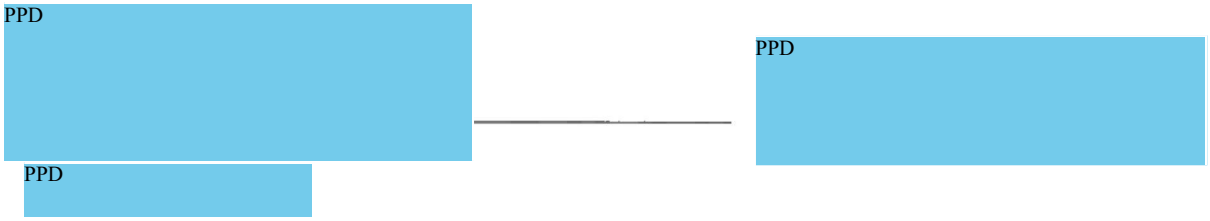
Sponsor Signatory:



Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Version**	**Date**
Amendment 2.0	Version 3.0	25 Feb 2022
Amendment 1.0	Version 2.0	19 Jul 2021
Original Protocol	Version 1.0	03 Sep 2020

Amendment 2.0 (25 Feb 2022)

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Formatting, grammar, and logical errors were corrected throughout the document.	To maintain consistency throughout the document.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints, and Section 9.4.7 Efficacy Analyses	"Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 (Visits 2-9) based on eDiary (RESQ-eDiary), including splits into day- and nighttime evaluations" added to list of endpoints. Splits into day- and nighttime evaluations also added for "Percentage of heartburn-free 24-hour days during the Weeks 1-8 (Visits 2-9) based on eDiary (RESQ-eDiary)"".	Clarification added that several degrees of symptom relief are of interest, as well as day- and nighttime evaluations, to describe efficacy.
Section 1.3 Overall Schedule of Assessment (Table 1),	Symptom diary provision/training/ review is removed from the Screening visit.[0] Footnote 10 updated to include the following bold text: Patients will be trained on how to complete the symptoms diary **during Visit 2 and the actual diary will be provided at Visit 2**.	Footnote updated for clarity
Section 1.3 Overall Schedule of Assessment (Table 1), Section 5	Footnote 14 added to include the following: For the screening only, 7 days are counted as 7 working days and not calendar days. Non-working days are weekend (Saturday, Sunday) and any country specific public holiday. Footnote 15 updated to include the following: Endoscopy video/digital image taken prior to ICF signature can be used as index endoscopy for the enrollment, if taken within 7 **working**	Footnotes updated for clarity

Section # and Name	Description of Change	Brief Rationale
	days of the planned treatment day. **For patients invited for screening upper endoscopy based on their past medical history (see Section 5), the ICF will be signed prior to the endoscopy. The screening procedures must start with endoscopy and in case the patient doesn't show LA grade C or D erosions, the rest of the screening procedures must not be conducted. This screening endoscopy must be obtained within 7 calendar days of planned randomization.**	
Section 4.1 Study Design	Following text deleted: ~~The endoscopy assessments before the screening visit is a pre-study investigation, while the endoscopy assessment after 4 weeks of treatment is part of the study assessments.~~	As per FDA feedback
Section 5 Study Population	Section is updated by adding the following: The patients possibly eligible will be identified as the following: 1. Patients identified during their routine endoscopy. • Patients must have erosive esophagitis identified during the routine endoscopy, before being considered for study screening (prior to signing the ICF). • This routine endoscopy will also serve as the index endoscopy in the study and the report should contain the endoscopy findings using the Los Angeles (LA) classification. • This routine endoscopy must be obtained within 7 working days of planned randomization, please refer to Inclusion criterion #4. 2. Patients invited for screening upper endoscopy based on their past medical history (both criteria must be met): a) LA grade C or D disease within the past 5 years before screening, demonstrated with endoscopy (endoscopy report issued by a	Text updated to clarify criteria for patients identified during their routine endoscopy and for patients invited for screening endoscopy based on their past medical history.

Section # and Name	Description of Change	Brief Rationale
	gastroenterologist/endoscopist is accepted) b) In Investigator's judgement the patient presents clear symptom relapse: patient may be treated with PPI, discontinued PPI treatment (patient's decision) or treatment naïve. For patients invited for screening upper endoscopy, the ICF will be signed prior to the endoscopy. The screening procedures must start with endoscopy and in case the patient doesn't show LA grade C or D erosions, the rest of the screening procedures must not be conducted. This screening endoscopy must be obtained within 7 working days of planned randomization The index/screening endoscopy video/digital image will be anonymized and saved for central storage. Imaging data must meet quality standards for adequate LA grading and must be accompanied by a report and videos/digital images to allow retrospective analysis of the endoscopy findings.	
Section 5.1 Inclusion Criteria	Inclusion Criteria #4 updated to include Gastro-esophageal reflux disease with endoscopically confirmed **erosive** esophagitis. • LA grade C or D ≤ 7 **working** days before randomization (with or without historical PPI treatment) or • LA grade A or B ≤ 7 **working** days before randomization o history of treatment with standard healing course of PPI* for minimum of 8 weeks prior to screening and ≤ 7 **working** days of non-treatment during this period**. Additionally, it is clarified that "Non-treatment	Inclusion criteria updated for clarity

Section # and Name	Description of Change	Brief Rationale
	days are counted from the last day of **standard healing course of** PPI therapy until endoscopy **used for eligibility assessment** demonstrating erosive esophagitis due to GERD"	
Section 5.2 Exclusion Criteria	Following note added to Exclusion Criteria #12: Patients with positive anti-HBcAg along with negative HBsAg at screening will not be excluded IF they have a positive local anti-HBs test results not older than 6 months and active HBV infection has been ruled out by the Investigator.	Exclusion criteria updated for clarity
Section 8.2 Efficacy Assessments	Following text is modified: **All videos and digital images will be centrally reviewed retrospectively. This review will include reassessment of the LA grading and other findings which may constitute exclusion criterion.** ~~Central reading of the videos/digital images is not planned. However, if Sponsor deems necessary to implement central reading, based on unexpectedly high healing rates, t~~ The central reading evaluation will override the investigators evaluations. **Data obtained from patients deemed to have been ineligible for study enrollment following the retrospective analysis will be excluded from the per protocol analysis.**	Per FDA feedback
Section 8.5 Treatment of Overdose	Text updated to display that "In the case of suspected overdose, the patient should be monitored. Lansoprazole is not significantly eliminated ~~removed from the circulation~~ by hemodialysis. ~~In the event of over-exposure, treatment should be symptomatic and supportive.~~	Text updated to reflect changes as per lansoprazole SmPC
Appendix 9 Medications that may Interact with X842 or Linaprazan	Footnote added for hormone based contraceptives to include the following: Except for patients using hormonal contraception defined in Exclusion criterion #1	Footnote added for clarity.
Appendix 10 COVID-19 Specifics	Publication date updated for the EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic. Publication date updated for the FDA	Reference list updated for the updated versions of EMA and FDA guidance.

Section # and Name	Description of Change	Brief Rationale
	Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency.	
Section 11 References	Lansoprazole SmPC updated link added	Reference list updated for the updated versions of lansoprazole SmPC.

Amendment 1.0 (19 Jul 2021)

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Several different medical terms are used to describe the underlying disease, such as "**reflux esophagitis**", "**erosive GERD**", "**erosive esophagitis**". As per FDA advice, used the term "**erosive esophagitis due to GERD**" throughout the document.	As per Competent Authority suggestion.
Throughout the document	The word "**participant**", **"patient**" and "**subject**" are used in the document**.** For clarity and consistency these terms are replaced with "**patient**"**.**	The study will be conducted in patients with GERD; hence, for clarity and consistency, "participant" and "subject" are changed to "patient".
Throughout the document	Study Intervention replaced with Study Drug	Study Intervention replaced with Study Drug for consistency.
Throughout the document	Screening assessment days were changed from "**5 days**" to "**7 days**".	Screening day changed as per the Sponsor request.
Throughout the document	Study monitor replaced with CRA	For clarity.
Throughout the document	Formatting, grammar, and logical errors were corrected throughout the document.	To maintain consistency throughout the document.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis (Treatment Groups and Duration)	The study drugs should be taken with 100 mL of noncarbonated water ~~irrespective of~~ at least 30 minutes prior to meals.	Updated for clarity.
Section 1.3 Overall Schedule of Assessment Table 1	Screening period "**Day -0**" changed to "**Day 0**". Daily symptom diary (RESQ-eDiary) completion by patient is removed for screening period. Footnote is revised to indicate the following: 5. Hematology, blood chemistry, coagulation (central laboratory), urinalysis (~~local laboratory~~ at site). Serum gastrin at screening and at Visit 5 (central laboratory). 6. *H. pylori* will be analyzed in central laboratory from serum and the result will not be needed for randomization.	Updated for clarity. Deleted per RESQ-eDiary schedule change in Table 1. Footnote updated for clarity.
Section 1.3 Overall Schedule of Assessments Table 1 (footnote #14), Section 5, Section 8.2 and Section 10.1.3	Amendment made to indicate that endoscopy results in both video and Image format is acceptable by adding the term **digital images** along with video i.e., videos/**digital images.**	Text updated for clarity.
Section 2.1 Background	The expansion of AUC was revised from "**area under the curve**" to "**area under the concentration-time curve**"	Updated for clarity.
Section 2.3.1 Summary of Risk Management, Section 10.1.4 Patient Identification Card, Section 10.1.5 Patient Data Protection and Section 10.1.8 Archiving	"**Patient information card**" is replaced with "**Patient Identification**" card.	Patient Identification card was submitted in all countries to the Authorities.
Section 5.1 Inclusion Criteria	**Criterion #4:** Gastro-esophageal reflux disease with endoscopically confirmed esophagitis: LA grade C or D ≤ ~~5~~7 days before randomization (with or without historical PPI treatment)	**Criterion #4:** As per Competent Authority suggestion, to exclude lansoprazole from

Section # and Name	Description of Change	Brief Rationale
	or LA grade A or B ≤ ~~5~~7 days before randomization and history of treatment with standard healing course of PPI* for minimum of 8 weeks prior to screening and ≤ ~~5~~7 days of non-treatment during this period~~—~~**. and at least partial symptom response during the minimum of 8 weeks of PPI treatment. Note: ~~p~~Partial symptom response is defined as a clear symptom improvement (heartburn or regurgitation) after start of the PPI treatment course. To qualify, the patient's response must be YES to the Investigator´s standardized question to the patient: Did you feel a clear symptom improvement in ~~(~~heartburn or regurgitation~~)~~ after you started the PPI treatment course? ~~Patient´s response must be YES or NO)~~ * All PPIs EXCEPT lansoprazole ** Non-treatment days are counted from end day of PPI therapy until endoscopy demonstrating erosive esophagitis due to GERD." **Criterion #5:** Willing and able to comply with all aspects of the protocol (including PK sampling, capsule swallowing, diary completion, etc.)	the primary treatment. Change in 5 days to 7 days was done based on extension of screening period. **Criterion #5:** PK sampling is added for completeness of procedures.
Section 5.2 Exclusion Criteria	**Criterion #1:** Female patients of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using one of the following adequate methods of contraception during dosing and for at least seven (7) days after the last dose of study medication: Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and	**Criterion #1:** A note regarding female patients who are using hormonal contraceptive included for adequate control of contraception

Section # and Name	Description of Change	Brief Rationale
	withdrawal are not acceptable methods of contraception Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking the first dose of study treatment. In case of oophorectomy alone, only when the reproductive status of the patient has been confirmed by follow-up hormone level assessment. Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient. Placement of a non-hormonal IUD Double barrier methods of contraception: condom in combination with occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/vaginal suppository Note: Patients who are already on hormonal contraceptives prior to study enrollment must agree to: replace hormonal contraception with double barrier method or use double barrier contraception method in addition to the hormonal contraceptives **Criterion #2:** Female patients of non-childbearing potential not requiring a contraceptive method, are defined as: •Pre-menopausal females with a documented tubal ligation or hysterectomy; or •Post-menopausal females defined as at least 12 months of amenorrhea (without an alternative medical cause) and confirmed with simultaneous serum follicle stimulation hormone (FSH), consistent with post-menopausal status according to central laboratory ranges ~~do not need to use a contraceptive method~~. Patients who do not meet one of these two criteria above will be considered being of	**Criterion #2:** text added for clarification

Section # and Name	Description of Change	Brief Rationale
	childbearing potential, and are excluded unless using one of the adequate contraceptive methods defined in Exclusion Criterion #1. **Criterion #8:** Presence of esophageal ulcer, stricture, Barrett´s esophagus or suspected esophagitis secondary to infection, inflammatory disease, ingestion of erosive chemicals or history of any surgical or medical condition which might significantly alter the GERD status or the absorption, distribution, metabolism or excretion of drugs. The Investigator is to be guided by evidence of any of the following: history of major gastrointestinal surgery such as gastrectomy, gastroenterostomy, bowel resection or transjugular intrahepatic portosystemic shunt (TIPS) **Criterion #11:** Any clinically significant laboratory parameter outside reference value that, in the opinion of the Investigator, may suggest a new or insufficiently understood disease, may present an unreasonable risk to the patient as a result of his/her participation in the study, or may interfere with study assessments. Any of these screening laboratory tests results are exclusionary: Serum ALT or AST > 1.5 times the upper limit of normal (ULN) for the central laboratory conducting the test Serum Total Bilirubin > 1.5 x ULN for the central laboratory conducting the test Serum Creatinine > 1.5 x ULN for the central laboratory conducting the test Estimated glomerular filtration rate ≤ 59 mL/min (calculated using the Modification of Diet in Renal Disease equation) **Criterion #13:** After 10 min supine rest at the time of screening, any vital signs values outside the following ranges:	**Criterion #8:** Amended to add medical conditions which might significantly alter the GERD or the absorption, distribution, metabolism or excretion of study drug. **Criterion #11:** As per Competent Authority suggestion to include laboratory test results exclusion criteria. **Criterion #13:** Lower limit added to cover both

Section # and Name	Description of Change	Brief Rationale
	• Systolic blood pressure (BP) > 160 mmHg or < 90 mmHg • Diastolic BP > 100 mmHg or < 60 mmHg • Heart rate < 40 or > 95 beats per min	extreme of the BP, necessary aspect for selecting patient.
Section 6.3.1 Randomization	Randomization ~~cap should~~ will be set as approximately ~~40%~~ 50% of patients with LA grade A and B ~~allowing at least 60% of patients being randomized from~~ and approximately ~~60%~~ 50% of patients ~~being~~ with LA grade C or D.	Updates are done as per Competent Authority suggestion.
Section 6.8 Intervention After the End of the Study	There will be no treatment with X842 or lansoprazole available, provided by Sponsor, after the End of Study participation. Following discontinuation of study treatment some patients may need additional therapy for their erosive esophagitis due to GERD. The Investigator should ensure patients re-establish care with a physician during the open-label treatment period in order to avoid a lapse.	As per Competent Authority suggestion, updates done to avoid relapse.
8.2 Efficacy Assessments	Upper endoscopy for the examination of esophagus will be used to confirm patient eligibility as well as the confirmation of the primary endpoint. Imaging data must meet quality standards for adequate LA grading and must be accompanied by a report and videos/digital images to allow retrospective analysis of the endoscopy findings.	Statement included to ensure quality imaging for better assessments
Section 8.3.2 Weight and BMI	Weight will be measured wearing light clothes and without shoes as designated on the SoA. The method of weight assessment will be the same across all visits. Body mass index (BMI) unit is kg/m^2 and calculated as weight in kg and height in meter.	Updates are done as per the Competent Authority suggestion.
Section 8.3.5 Clinical Safety Laboratory Assessments (Laboratory parameter table and footnotes)	"**Urine drug abuse screen**" is moved from "Urinalysis (dip stick)" section to "Others" section in the table Footnote is amended accordingly.	As urine drug abuse screen is not a dip stick, footnote was amended for clarity.
8.3.7 Reflux Related Symptoms Assessed Based on PRO	Reflux related symptoms will be also assessed based on a modified RESQ-eDiary; an electronic symptom diary developed for use in	Modified RESQ-eDiary added for clarity and "every

Section # and Name	Description of Change	Brief Rationale
	partial responders to PPI. RESQ-eD has three Domains (i.e. Heartburn, Other GERD signs/symptoms and Regurgitations/Reflux) and eight Items. Patients will be asked to report ~~twice daily~~ every 12-hours, once before the morning dose and once before the evening dose of the IMP.	12-hours" was added to be more specific in reporting time.
8.3.8 Reflux Related Symptoms Assessed by Investigator	Section is updated by adding following: The potential frequency is defined as 7-graded Likert scale: • All of the time; • Most of the time; • Quite a lot of the time; • Some of the time; • A little of the time; • Hardly any of the time; • None of the time.	Text updated to define frequency of symptoms on 7-graded Likert scale.
Section 8.3.9 Pharmacokinetic Samples and Analysis	PK samples will be collected 12 hours after the previous study drug dose administration or as close to this timepoint as possible, but always pre-dose (close before the first and the second dose administration at Days 7, 14 and 28).	Updated to clarify pre-dose.
Section 8.4.1.3 - Table 2 (Liver Event and Laboratory Trigger Definitions)	A. LIVER LABORATORY TRIGGERS is changed from "~~3×ULN < ALT or AST ≤ 5× ULN~~ ~~1.5 ×ULN < TBL ≤ 2×ULN~~" to "ALT or AST > 3 × ULN, but ALT and AST ≤ 5 × ULN TBL > 1.5 × ULN, but TBL≤ 2 × ULN".	Liver laboratory range revised to clarify ULN.
8.4.6 Reporting of Serious Adverse Events	Following text changed from "~~Serious adverse events reporting should be performed by the Investigator within 24 hours of awareness via the eCRF or by e-mailing a copy of an SAE Form. All available information regarding the SAE should be entered in the AE Log for the specific patient. The SAE report is reviewed by a designated person at Parexel to ensure that the report is valid and correct. For fatal or life-threatening SAEs where important or relevant information~~	Reporting of serious adverse events updated as per current practice at Parexel.

Section # and Name	Description of Change	Brief Rationale
	~~is missing, immediate follow-up is undertaken and queries to the site are raised. Investigators or other site personnel should inform designated person of any follow-up information on a previously reported SAE immediately but no later than the end of the next business day of when he/she becomes aware of it.~~ ~~If an SAE report is updated, the designated study personnel will be informed.~~ ~~The appointed Medical Monitor will provide his/her causality assessment and make an expectedness assessment once the report is judged to be complete. The reference document for definition of expectedness is the Reference Safety Information in the current version of IB.~~ ~~If any additional documentation is required (e.g. hospital discharge letter, autopsy report, etc.), designated person will request this information from the study site.~~ ~~In case the eCRF cannot be accessed, the SAE should be reported by manually completing the paper SAE Form, provided in the investigator site file (ISF). completed, signed and dated paper SAE Form should, within 24 hours, be scanned and e-mailed to:~~ ~~PPD~~ ~~Telephone: PPD~~ ~~E-mail: PPD~~ ~~A copy be e-mailed to Parexel at: CinclusADR@parexel.com".~~ **To** On discovery, all SAE/AESIs should be immediately reported (latest within 24 hours of knowledge of the event) to Parexel Safety Services by: Entering the AE in the appropriate section (AE page and/or SAE page) of the eCRF, indicating that the event is considered serious, and	

Section # and Name	Description of Change	Brief Rationale
	providing all the details per the eCRF completion guidelines **and** Completing the SAE report form and e-mailing/faxing the documents to Parexel Safety Services as per details below: France (Paris) Mailbox: 249403_Safety@parexel.com France (Paris) Fax numbers: +33 1 44 90 32 75 or +33 1 44 90 35 34 In the event that the site is unable to complete the SAE form or eCRF entry to report the event within 24 hours of their knowledge of the event, the investigators may report the SAE over the telephone via the SAE answering service, and then provide the completed SAE form via **(fax or email)**, or complete the eCRF entry of the event (within the next 24 hours). If questions arise regarding the reporting procedures or the specifics of the reporting of an event, sites may call (English) utilizing the following numbers: Paris: +33 1 44 90 32 90 In case the eCRF cannot be accessed, the SAE should be reported by manually completing the paper SAE Form, provided in the investigator site file (ISF). The SAE report is reviewed by a designated person at Parexel to ensure that the report is valid and correct. For fatal or life-threatening SAEs where important or relevant information is missing, immediate follow-up is undertaken and queries to the site are raised by Parexel. Investigators or other site personnel should inform designated person of any follow-up information on a previously reported SAE immediately but no later than the end of the next business day of when he/she becomes aware of it. If an SAE report is updated, the designated study personnel will be informed. If any additional documentation is required	

Section # and Name	Description of Change	Brief Rationale
	(e.g., hospital discharge letter, autopsy report, etc.), designated person will request this information from the study site.	
9.2 Sample Size Determination	CCI [redacted]	Text updated for clarity.

Section # and Name	Description of Change	Brief Rationale
Section 9.4	The following duplicated text was removed: ~~The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in the SAP, which will be approved and singed prior to database lock.~~ ~~The primary study objective is to estimate the X842 dose for Phase 3 study with good precision, and hence comparison of different doses of X842 to the active comparator arm (lansoprazole 30 mg) will not involve any formal statistical testing.~~ ~~The primary analysis evaluating the dose-response relationship based on different doses of X842, as well as secondary analyses will additionally assess the two subgroups, eGERD LA grade C or D and eGERD LA grade A or B (partial responders to PPI treatment).~~ ~~All data measured on a continuous scale will be presented using summary statistics. Summary statistics is defined as number (N), arithmetic mean, standard deviation (SD), median, minimum Q1, Q3 and maximum value. Where appropriate 95% confidence intervals will be presented.~~ ~~Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual patient data will be listed by patient number, treatment, and, where applicable, by assessment time.~~	Duplicated text removed.
10.1.9 Study and Site Closure	The following was added in this section as amendment:	Study stopping rules are added according

Section # and Name	Description of Change	Brief Rationale
	The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. The study may be placed on hold for evaluation of possible risk to patients, prior to decision as to whether to terminate the study if any of the following criteria are met: At least 3 patients experience a similar unexpected AE, which is assessed as severe and is probable/possible related to the IMP. The occurrence of an SAE, if considered probable/possible related to the IMP. A study termination will be initiated pending the outcome of any SAE investigation; termination will be based on the circumstances surrounding the event and findings with unblinding of the Sponsor medical monitor, if necessary. The study will be discontinued for any of the following reasons: If overall 5 (five) X842-treated patients develop the same type of AESI and the frequency is at least 2 × higher than in the comparator group. If 3 (three) X842-treated patients meet Hy's Law criteria (≥ 3 × ULN for ALT or AST with total bilirubin ≥ 2 × ULN and no other explanation for these elevations). If one or more clinically significant, life-threatening, or significantly disabling/incapacitating events that are likely related to X842 and that, in the opinion of the Investigator in consultation with the Sponsor, may constitute sufficient reason to stop the study. If the Sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.	to FDA suggestion

Table of Contents

List of Tables

List of Figures

1 Protocol Summary

1.1 Synopsis

Protocol Title: A randomized double-blind, double dummy, active comparator-controlled dose-finding study in patients with erosive esophagitis due to gastro-esophageal reflux disease (GERD) Los Angeles grade C or D, and patients with at least partial symptom response but endoscopically still unhealed after 8 weeks history of standard treatment healing course with proton-pump inhibitor (PPI), to investigate safety, tolerability, and healing rates after 4 weeks treatment of X842 or lansoprazole, and symptom pattern during subsequent 4 weeks treatment with lansoprazole

Sponsor Study No.: CX842A2201

Phase: Phase 2

Sponsor: Cinclus Pharma AG
Gartenstrasse 101
CH-4002 Basel, Switzerland

Study Rationale:

This is a Phase 2, double-blind study in patients with erosive esophagitis due to GERD Los Angeles (LA) grades C or D, and in patients with at least partial symptom response but still endoscopically unhealed (LA grades A or B) after 8 weeks history of standard treatment healing course with PPI, designed to support dose selection for Phase 3. The pronounced acid control of X842 is assumed to provide high endoscopic healing rates already after 4 weeks treatment course. The four dose levels of X842 are selected based on data from the Phase 1 studies where the 50 mg twice daily (BID) dose displayed an acid control slightly stronger than observed for standard PPI. The dose selection for Phase 3 will be based on the proportion of endoscopic healing following each dose of X842, the respective safety data and the pharmacokinetic (PK) profile. Lansoprazole will serve as an active comparator.

Objectives and Endpoints

Objectives	Endpoints
Primary	
The primary objective of the study is to support dose selection for X842, through assessment of healing of erosive esophagitis due to GERD after 4 weeks of treatment.	Healing of erosive esophagitis due to GERD based on endoscopic assessment after 4 weeks of double-blind treatment.
Secondary	
Evaluate the safety and tolerability of the four dose levels of X842 and lansoprazole, where lansoprazole will serve as the active comparator.	Physical examination, weight, body mass index (BMI), vital signs, electrocardiogram (ECG) recordings, safety laboratory measurements (hematology/clinical chemistry/urinalysis), adverse event (AE), treatment emergent adverse event (TEAE), adverse event of special interest (AESI), serious adverse event (SAE) reporting, concomitant medication(s).
Evaluate the reflux related symptom pattern during the initial 4 weeks treatment with four dose levels of X842 and with lansoprazole, and the symptom pattern during the subsequent additional 4 weeks (Weeks 5-8) open-label treatment with lansoprazole 30 mg QD	• Percentage of heartburn-free 24-hour days during the Weeks 1-8 (Visits 2-9) based on eDiary (RESQ-eDiary), including splits into day- and nighttime evaluations. • Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 (Visits 2-9) based on eDiary (RESQ-eDiary), including splits into day- and nighttime evaluations. • Investigator assessment of symptom at Weeks 1-8 (Visits 2-9) • Reflux related symptoms as measured by change from baseline in QOLRAD score assessed after 1, 2, 4 and 8 weeks of treatment
Exploratory	
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

Overall Design:

The study will be conducted in multiple centers in Europe and the US. This will be a randomized, double-blind, active comparator-controlled study with a parallel group design including four arms with X842 and one arm with lansoprazole. Pharmacokinetic (PK) blood sampling pre-dose, before the first and the second dose administration will be performed at Day 7, Day 14 and Day 28 visits in all patients. Approximately 240 patients with erosive esophagitis due to GERD LA grade C or D and patients with erosive esophagitis due to GERD LA grade A or B with at least partial symptom response but still endoscopically unhealed after 8 weeks history of standard treatment healing course with PPI, will be randomized in order to have 200 evaluable patients.

Randomization to one of the treatments with X842 twice daily (BID) 25 mg, 50 mg, 75 mg, 100 mg, or lansoprazole 30 mg once daily (QD) will be based on a 1:1:1:1:1 scheme. One site cannot enroll more than 20% of the overall number of patients (48 patients).

The duration of each patient's participation in the study, including screening, blind treatment period and open-label treatment period will be approximately 60 days. The patients will be randomized for 4 weeks (28 days, -2/+5 days) double-blind treatment and will be provided with investigational medicinal product (IMP) for 35 days (including one additional blister pack dispensed at Visit 2/Day 0) to allow for treatment up to the visit window. All patients will have an endoscopic evaluation after 4 weeks treatment. Following the endoscopic evaluation, all patients will receive subsequent 4 weeks open-label treatment with lansoprazole 30 mg QD. Repeated symptom evaluation to detect symptom pattern will be assessed during this period.

Randomization ratio	TREATMENT GROUP	Morning capsule	Morning tablet 1	Morning tablet 2	Evening tablet 1	Evening tablet 2
1	X842 (BID) 25 mg	placebo	25 mg	placebo	25 mg	placebo
1	X842 (BID) 50 mg	placebo	50 mg	placebo	50 mg	placebo
1	X842 (BID) 75 mg	placebo	50 mg	25 mg	50 mg	25 mg
1	X842 (BID) 100 mg	placebo	50 mg	50 mg	50 mg	50 mg
1	Lansoprazole (QD) 30 mg	30 mg	placebo	placebo	placebo	placebo

Number of Patients:

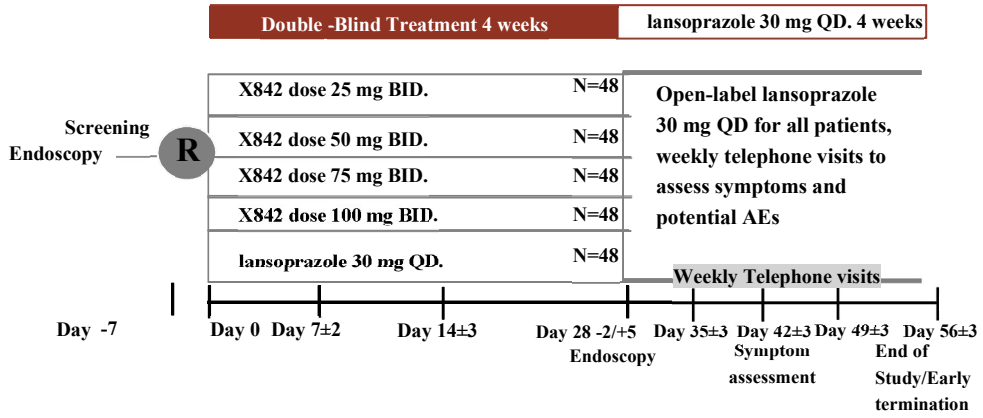
The number of patients in the study will be approximately 240; 48 patients in each treatment arm.

Treatment Groups and Duration:

Four doses of X842 (25 mg, 50 mg, 75 mg, 100 mg, and dummies) will be administered as tablets twice daily. The active comparator lansoprazole 30 mg and its dummy will be administered as capsules once daily in the morning. The study drugs should be taken with 100 mL of noncarbonated water at least 30 minutes prior to meals. The duration of double-blind treatment will be 28 days -2/+5 days. To blind treatment, each patient will receive 2 tablets (containing doses of X842 or its dummy) and one capsule (containing lansoprazole or its dummy) in the morning and 2 tablets (containing doses of X842 or its dummy) in the evening.

1.2 Schema

Figure 1 Study Design



BID = Twice Daily; QD = Once Daily; R = Randomization

1.3 Schedule of Assessments (SoA)

Details on procedures and timing of assessments are presented in Table 1.

Table 1 Overall Schedule of Assessments

Visit	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Tel Visit 6	Tel Visit 7	Tel Visit 8	Visit 9 End of Study / Early Termination
Assessment/Study day	**Day -7[14] to Day 0**	**Day 0**	**Day 7 ±2 days**	**Day 14 ±3 days**	**Day 28 -2/+5 days**	**Day 35 ±3 days**	**Day 42 ±3 days**	**Day 49 ±3 days**	**Day 56 ±3 days**
Assessment/Study week		**Randomization**	**Week 1**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
	Screening Period	**Blinded Treatment Phase**				**Open-Label Phase**			
Informed consent	X								
Demographics	X								
Inclusion/exclusion criteria	X	X							
Medical/surgical history [1]	X								
Weight, height [2]	X				X				X
Complete physical examination	X				X				X
Drugs of abuse	X								X
Viral serology testing [3]	X								
Vital signs [4]	X		X		X				X
12-lead ECG evaluation	X		X		X				X
Safety laboratory [5]	X		X		X				X
H. pylori testing [6]	X								

Visit	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Tel Visit 6	Tel Visit 7	Tel Visit 8	Visit 9 End of Study / Early Termination
Assessment/Study day	**Day -7[14] to Day 0**	**Day 0**	**Day 7 ±2 days**	**Day 14 ±3 days**	**Day 28 -2/+5 days**	**Day 35 ±3 days**	**Day 42 ±3 days**	**Day 49 ±3 days**	**Day 56 ±3 days**
Assessment/Study week		**Randomization**	**Week 1**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
	Screening Period	**Blinded Treatment Phase**				**Open-Label Phase**			
Pregnancy test [7]	X				X				X
Randomization		X							
Patients provided with study drugs for blinded phase		X	X	X					
Patients provided with Lansoprazole 30 mg for open-label phase					X				
PK blood sampling [8]			X	X	X				
Upper endoscopy	X[15]				X				
Symptom evaluation using QOLRAD Heartburn [9]		X	X	X	X				X
Daily symptom diary (RESQ-eDiary) completion by patient		X	X	X	X	X	X	X	X
Symptom diary provision/training/ review[10]		X	X	X	X	X	X	X	X

Visit	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Tel Visit 6	Tel Visit 7	Tel Visit 8	Visit 9 End of Study / Early Termination
Assessment/Study day	**Day -7[14] to Day 0**	**Day 0**	**Day 7 ±2 days**	**Day 14 ±3 days**	**Day 28 -2/+5 days**	**Day 35 ±3 days**	**Day 42 ±3 days**	**Day 49 ±3 days**	**Day 56 ±3 days**
Assessment/Study week		**Randomization**	**Week 1**	**Week 2**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
	Screening Period	**Blinded Treatment Phase**				**Open-Label Phase**			
Symptom assessment by Investigator [11]	X	X	X	X	X	X	X	X	X
AE reporting [12]	X	X	X	X	X	X	X	X	X
Prior/concomitant medications [13]	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; ECG, electrocardiogram; ICF, informed consent form; LA, Los Angeles; PK, pharmacokinetic.

1. Including smoking (current status), alcohol consumption, and intake of drug of abuse.
2. Height only at screening
3. Human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B core antigen (anti-HBcAg), antibody to hepatitis C virus (anti-HCV) testing at central and/or local laboratory. Patient should discontinue the study if result from central laboratory is positive.
4. Systolic and diastolic blood pressure (BP) [mmHg], heart rate [beats per minute], body temperature and respiratory rate [per minute].
5. Hematology, blood chemistry, coagulation (central laboratory), urinalysis (at site). Serum gastrin at screening and at Visit 5 (central laboratory).
6. *H. pylori* will be analyzed in central laboratory from serum and the result will not be needed for randomization.
7. Women of childbearing potential only. Serum pregnancy test at central laboratory at screening and urine pregnancy test at clinic/investigational site prior to the dose administration at Visit 5, and at End of Study / Early Termination.
8. PK measured in all patients just before the first and the second dose on the day of the visit. At all PK sampling occasions, the time since latest study drug administration must be noted in the case report form (CRF). Pharmacokinetic samples will be collected 12 hours after the previous study drug dose administration or as close to this timepoint as possible, however, still pre-dose.
9. QOLRAD assessment must be done pre-dose. QOLRAD will be completed by patients during site visits at Visit 2, 3, 4, 5 and 9.
10. Patients will be trained on how to complete the symptoms diary during Visit 2 and the actual diary will be provided at Visit 2.

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11. At each visit, Investigator should assess the severity of patients' heartburn, regurgitation and dysphagia in the 7 days prior to the visit. The assessment will include both the severity grade and the frequency of symptoms. Symptoms are scored as follows: none (no complaints), mild (aware of symptom, but easily tolerated), moderate (discomforting symptom, sufficient to cause interference with normal daily activities and/or sleep), severe (incapacitating symptom, with inability to perform normal daily activities and/or sleep)
12. Collection of AEs will start directly after the informed consent form (ICF) has been signed. During the screening period, only AEs related to study procedure will be reported.
13. For definitions of prior and concomitant medication, see Section 8.1.6.
14. For the screening only, 7 days are counted as 7 working days and not calendar days. Non-working days are weekend (Saturday, Sunday) and any country specific public holiday.
15. Endoscopy video/digital image taken prior to ICF signature can be used as index endoscopy for the enrollment, if taken within 7 working days of the planned treatment day. For patients invited for screening upper endoscopy based on their past medical history (see Section 5), the ICF will be signed prior to the endoscopy. The screening procedures must start with endoscopy and in case the patient doesn't show LA grade C or D erosions, the rest of the screening procedures must not be conducted. This screening endoscopy must be obtained within 7 working days of planned randomization.

2 Introduction

2.1 Background

Gastro-esophageal reflux disease (GERD) is a common chronic disorder with the prevalence highest in North America and Europe, where at least weekly reflux symptoms range from 10 to 30%. Epidemiologic data are limited but suggest a lower prevalence in Asia [1], although prevalence is increasing in this region and other developed countries [1]. A universally accepted definition of treatment success in GERD is not available [1].

A new class of molecules, potassium-competitive acid blockers (P-CABs), presents a new mode of action, that, in principle, allows full acid control both day and night. Such acid inhibitory properties in humans are likely to allow for successful treatment of patients with erosive esophagitis due to GERD Grade C and D, the most acid-sensitive GERD sub-population. Linaprazan, the main metabolite of X842, has shown to provide effective acid control in humans [3, 4].

The study drug, X842, shows a slower uptake after oral administration, compared to after oral administration of linaprazan. This results in a lower maximum concentration (C_{max}) of linaprazan after administration of X842. This should translate into a lower load of linaprazan to the liver and to a prolonged control of intragastric acidity.

The solubility of both linaprazan and X842 is pH dependent and increases exponentially at pH values below the pKa (6.1 for linaprazan and 5.5 for X842). Previous studies have shown a decrease in C_{max} and area under the concentration-time curve (AUC) for linaprazan with repeated dosing [5].

The first-in-human (FIH) study of X842 (CX842A2101) [6] was performed with a suspension formulation to allow dosing per kg. A tablet formulation is developed and the data from studies on pharmacokinetic and pharmacodynamic properties of this formulation are used for dose selection for this Phase 2 study and to further develop the biomarker for intragastric pH control (CX842A2102, CX842A2103).

2.1.1 Investigational Medicinal Product

2.1.1.1 Drug description

CCI

[redacted]

CCI [redacted]

More details about IMP and lansoprazole are available in the IMPDs / Material Safety Data Sheet.

2.1.1.2 Indication

X842 is developed for the treatment of all patients with erosive esophagitis due to GERD LA grade C or D and of patients with at least partial symptom response but still endoscopically unhealed (LA grades A or B) after at least 8 weeks history of standard treatment healing course with proton-pump inhibitor (PPI).

2.1.1.3 Dosage

The dose levels of X842 to be tested in this study are 25, 50, 75 and 100 mg (25 and 50 mg tablets) given orally twice daily (BID) for 4 weeks.

2.1.1.4 Mechanism of action

CCI [redacted]

CCI [redacted]

oved properties has been developed [3, 4].

CCI [redacted]

2.1.1.5 Non-clinical toxicology

Male and female Sprague-Dawley (SD) rats were administered X842 single oral doses up to 250 mg/kg and repeated oral doses up to 150 mg/kg for 28 consecutive days followed by 4-week

recovery period. Male and female Beagle dogs were administered single oral doses of X842 up to 120 mg/kg and repeated oral doses up to 48 mg/kg for 28 consecutive days followed by a 28-day recovery phase.

No signs of treatment-related toxicity have been noted following single oral administration of X842 at dose levels of up to 250 mg/kg in SD rats. Some emesis has been seen at all dose levels investigated in dogs. However, this is a very common clinical sign in toxicity studies in dogs and is not regarded as having any toxicological relevance unless it is very pronounced and/or frequent. The maximum tolerated dose (MTD) following a single dose of X842 was above the maximum given doses of 250 mg/kg in rats and 120 mg/kg in dogs. In the 28-day repeat-dose study in rats and a study of fertility and early embryonic development in rats, the no observed adverse effect level (NOAEL) is considered to be 150 mg/kg in both genders. In the 28-day repeat-dose study in dogs the NOAEL is considered to be 48 mg/kg in both genders. In all instances, these were the highest doses given in each study.

In vitro (the Ames test and chromosome aberrations in Chinese hamster lung [CHL] cells) and in vivo (micronucleus test in rats) genotoxicity studies showed that X842 did not show mutagenic activity either with or without metabolic activation.

For detailed information, refer to the Investigator´s Brochure (IB) for X842.

2.1.1.6 Clinical experience

In the FIH study (single ascending dose [SAD] and multiple ascending dose [MAD]) the safety, tolerability and pharmacokinetic (PK) properties of X842 were evaluated [6]. The study concluded that X842 was well tolerated in single doses up to 4.0 mg/kg and multiple doses up to 2.0 mg/kg (the maximum dose administered in the MAD patients) and that the intragastric pH correlated with the plasma concentration of linaprazan during the time interval 0-24 hours after dose.

No serious adverse events (SAEs) nor adverse events (AEs) that led to withdrawal occurred after IMP administration and the number of patients experiencing AEs assessed as related to the IMP did not increase with an increasing dose. There were no clinically relevant findings or dose dependent mean changes over time in physical examinations, vital signs, electrocardiograms (ECGs) or laboratory parameters.

With regards to PK; PK parameters and dose linearity could not be calculated for X842 due to low plasma concentrations. For linaprazan, the relative bioavailability after fed and fasting conditions was determined from the AUC 0-24 hours (AUC_{0-24}) and C_{max}. No indication of food

interaction was seen, however there was a high variability in both AUC_{0-24} and in C_{max}. The exposure after a single administration of the highest dose (4.0 mg/kg) was lower than expected and the variability among patients was high. Dose linearity was shown for linaprazan for SAD Cohort 1-5, but not for SAD Cohort 6-7. The exposure in MAD Cohorts 2 and 3, given multiple doses of 2.0 mg/kg X842, was lower than expected after the first dose as compared to SAD Cohort 5 (2.0 mg/kg) and MAD Cohort 1 (1.0 mg/kg). High variability was also seen among patients. The reason for the non-dose linearity in SAD 6-7 and the low exposure MAD study was must likely the crystallization observed in the liquid formulation in the later cohorts.

In a subsequent Phase 1, open-label, two-period cross-over, no control, PK study of X842 in healthy volunteers, X842 was administered as i) two doses of 50 mg X842, separated by 24 hours and ii) two doses of 150 mg X842, separated by 24 hours. Each period is separated by at least 1 week. Data on this new tablet formulation showed that X842 was safe and well tolerated. The linaprazan plasma concentrations after dose Day 1 was increased in proportion to dose, while the concentrations following the dose administration Day 2 was lower than Day 1.

A Phase 1 PK/pharmacodynamics (PD) (intragastric pH over 48 hours) study on repeated BID dosing of 50 mg, 100 mg and 150 mg X842 during day 1 and 2 and once daily on day 3, has recently concluded recruiting. X842 was safe and well tolerated and no SAE occurred. A clear dose response was observed. The 50 mg dose provided acid control (intragastric pH > 4) during 68% of time while the corresponding figure for the 150 mg dose was above 90% of time. The PK value to predict the level of pH control was further explored. The pre-dose evening values showed low variability and were closely correlated to the level of pH control over time.

2.2 Study Rationale

This is a Phase 2, double-blind study in patients with erosive esophagitis due to GERD LA grades C or D, and in patients with at least partial symptom response but still endoscopically unhealed (LA grades A or B) after 8 weeks history of standard treatment healing course with PPI, designed to support dose selection for Phase 3. The pronounced acid control of X842 is assumed to provide high endoscopic healing rates already after 4 weeks treatment course. The four dose levels of X842 are selected based on data from the Phase 1 studies where the 50 mg BID dose displayed an acid control slightly stronger than observed for standard PPI. The dose selection for Phase 3 will be based on the proportion of endoscopic healing following each dose of X842, the respective safety data and the PK profile. Lansoprazole will serve as an active comparator.

2.3 Benefit/Risk Assessment

The majority of patients in this study are likely to experience medical benefit from their participation based on the properties of X842 and the active comparator. However, the lowest dose of X842 is selected to be slightly less efficacious than the active comparator, but still efficacious. Patients' safety and wellbeing is of utmost importance. Even though the toxicology studies and previous clinical studies have indicated a low toxicity with no major concerns at the dose levels studied, there is a clear need for attention to risk mitigation.

The study involves administration of a tablet formulation of X842 for humans, with the aim of generating data supporting dose selection for Phase 3. The BID dosing of 25, 50, 75 and 100 mg corresponding to a daily dose of 0.7 - 2.9 mg/kg [based on 70 kg body weight] in this study was selected based on data from the Phase 1 studies (CX842A2101, CX842A2102, CX842A2103). The NOAEL in the repeat-dose toxicity studies (rat and dog) was set equal to the highest doses given. Normally this highest dose would be increased in a repeat study of the same duration. In this instance however, results from the earlier studies strongly indicated that a saturation of exposure to both X842 and linaprazan occurred at all higher dose levels in both species, thus limiting the relevance of further increasing the dose and also justifying the use of the same dose levels in the repeat studies. The mean $AUC_{0\text{-}24}$ -values (males and females combined) noted at the stated highest dose levels (regarded as being the NOAELs) day 28 in the pivotal repeat-dose toxicity studies were 170 h*ng/mL and 2700 h*ng/mL for X842 and linaprazan, respectively, in rats and 270 h*ng/mL and 3200 h*ng/mL for X842 and linaprazan, respectively, in dogs. For linaprazan, it is therefore necessary to justify the safety of the chosen clinical doses of X842 by comparing the estimated exposure levels to linaprazan and X842 with those that have been shown to be safe and without any SAEs in previous clinical studies, rather than via a comparison with exposure values in the repeat-dose toxicity studies, in which even the highest dose levels of X842 given did not provoke any true toxic effects.

In all three Phase 1 studies, X842 was well tolerated in doses up to 4.0 mg/kg single dose, up to 2.0 mg/kg when administered as a once daily dose for five consecutive days, and in doses up to 150 mg BID for two days plus one additional dose on day 3. No SAEs occurred, and no adverse drug reactions (ADRs) led to withdrawal from the study. In the FIH study CX842A2101, X842 was given as a suspension at dose levels of 5.6 to 280 mg (0.08 to 4 mg/kg in a 70 kg individual). No PK parameters could be calculated for X842, as the plasma concentrations of this compound were very low or below the lower limit of quantification (LLOQ). It is anticipated that this will be the same in the current clinical study.

In the development program of X842's active metabolite, linaprazan, the SAD study with linaprazan included single doses up to 4.0 mg/kg which resulted in an AUC of 39200 h*ng/mL, which also was MTD [10]. Linaprazan itself was also administered to humans at safe and tolerable doses of up to 75 mg QD (1.1 mg/kg in a 70 kg human) for 56 days [3, 4].

Pharmacokinetic results from the all three Phase 1 studies on X842 and published data for linaprazan, strongly suggest that the PD-effect of linaprazan significantly lowers the bioavailability of linaprazan, thereby limiting the exposure of linaprazan seen 24 hours after the first dose administration.

The overall evaluation is that X842 doses 25 mg, 50 mg, 75 mg and 100 mg BID will be safe and well tolerated based on the three Phase 1 studies on X842 and supportive published linaprazan data on healthy volunteers and in patients.

2.3.1 Summary of Risk Management

Visits at the clinic/investigational site may be prolonged in case the Investigator finds it medically warranted for safety reasons. In cases of accidental overdose, standard supportive measures should be adopted as required. For further information regarding overdosing, refer to Section 8.5.

Each patient will be provided with a Patient Identification Card with information about the patient participation in a study, see Section 10.1.4.

The Principal Investigator at the research clinic/investigational site will ascertain that adequate facilities and procedures are available to handle emergency situations.

Besides the risks related to the IMP as described above, there may also be risks related to the repeated endoscopy after 4 weeks. Other medical devices, e.g., indwelling venous catheters, are used in routine medical care and the risk associated with their use is considered low and ethically justifiable. Study-specific evaluations and sampling procedures, like blood-pressure measurements using a blood pressure cuff and blood sampling, may cause transient discomfort but the risk is deemed to be low and ethically justifiable.

Linaprazan is the acid inhibitory metabolite of the X842 molecule. Linaprazan has been extensively studied and in a small number of patients increased LFTs were observed [3, 4] and careful evaluation concluded that the high C_{max} of linaprazan was the main reason for the LFT increase. The C_{max} of the metabolite linaprazan following administration of its prodrug X842 is reduced with about 75% and thereby minimizing the risk for hepatotoxicity. Overall, the combined safety data from the pre-clinical and clinical studies have not revealed any safety

issues that would outweigh the expected benefits of the study. While keeping the above-mentioned risk factors at a minimum level in order to not expose the patients participating in the study for risks that would not be ethically justifiable it is concluded that the planned study assessments are considered sufficient to meet the scientific and medical objectives of the study. It is therefore concluded that the potential benefits from the study will outweigh the potential risks for the treated patients.

More detailed information about the known and expected benefits and risks and reasonably expected ADRs of X842 is found in the IB.

3 Objectives and Endpoints

Objectives	Endpoints
Primary	
The primary objective of the study is to support dose selection for X842, through assessment of healing of erosive esophagitis due to GERD after 4 weeks of treatment.	Healing of erosive esophagitis due to GERD based on endoscopic assessment after 4 weeks of double-blind treatment.
Secondary	
Evaluate the safety and tolerability of the four dose levels of X842 and lansoprazole, where lansoprazole will serve as the active comparator.	Physical examination, weight, BMI, vital signs, electrocardiogram (ECG) recordings, safety laboratory measurements (hematology/clinical chemistry/urinalysis), adverse event (AE), treatment emergent adverse event (TEAE), adverse event of special interest (AESI), serious adverse event (SAE) reporting, concomitant medication(s).
Evaluate the reflux related symptom pattern during the initial 4 weeks treatment with four dose levels of X842 and with lansoprazole, and the symptom pattern during the subsequent additional 4 weeks (Weeks 5-8) open-label treatment with lansoprazole 30 mg QD.	• Percentage of heartburn-free 24-hour days during the Weeks 1-8 (Visits 2-9) based on eDiary (RESQ-eDiary) including splits into day- and nighttime evaluations. • Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 (Visits 2-9) based on eDiary (RESQ-eDiary), including splits into day- and nighttime evaluations. • Investigator assessment of symptom at Weeks 1-8 (Visits 2-9) • Reflux related symptoms as measured by change from baseline in QOLRAD score assessed after 1, 2, 4 and 8 weeks of treatment.
Exploratory	
CCI [redacted]	
CCI [redacted]	

4 Study Design

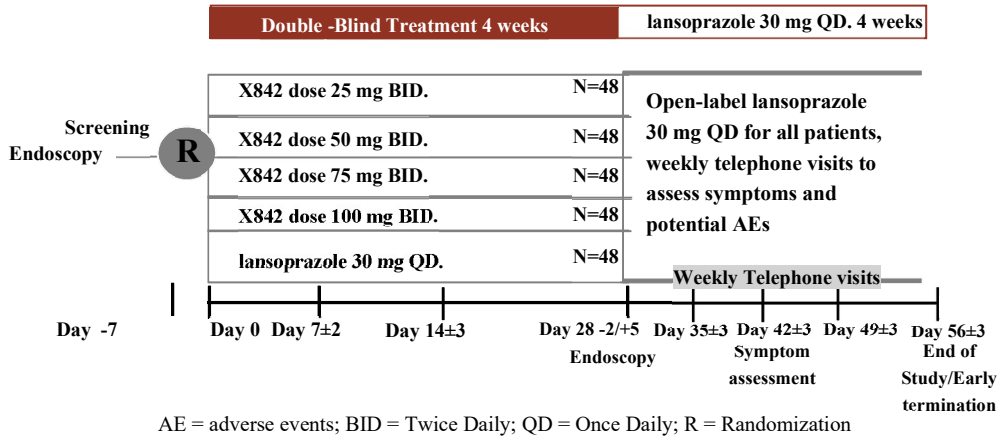
4.1 Overall Design

The study will be conducted in multiple centers in Europe and the US. This will be a randomized, double-blind, active comparator-controlled study with a parallel group design including four arms with X842 and one arm with lansoprazole. Pharmacokinetic (PK) blood sampling pre-dose, close before the first and the second dose administration will be performed at Day 7, Day 14 and Day 28 visits days in all patients. Approximately 240 patients with erosive esophagitis due to GERD LA grade C or D and patients with erosive esophagitis due to GERD LA grade A or B with at least partial symptom response but still endoscopically unhealed after 8 weeks history of standard treatment healing course with PPI, will be randomized in order to have 200 evaluable patients.

Randomization to one of the treatments with X842 BID 25 mg, 50 mg, 75 mg, 100 mg, or lansoprazole 30 mg once daily (QD) will be based on a 1:1:1:1:1 scheme. One site cannot enroll more than 20% of the overall number of patients (48 patients per site).

The duration of each patient's participation in the study, including screening, blind treatment period and open-label treatment period, will be approximately 60 days. The patients will be randomized for 4 weeks (28 days, -2/+5 days) of double-blind treatment and will be provided with IMP for 35 days (including one additional blister pack dispensed at Visit 2/Day 0) to allow for treatment up to the visit window. All patients will have an endoscopic evaluation after 4 weeks treatment. Following the endoscopic evaluation, all patients will receive subsequent 4 weeks of open-label treatment with lansoprazole 30 mg QD. Repeated symptom evaluation to detect symptom pattern will be assessed during this period. The study design is shown below (Figure 2).

Figure 2 Study Design



AE = adverse events; BID = Twice Daily; QD = Once Daily; R = Randomization

The study will comprise 6 visits at the site and 3 telephone visits. Based on the endoscopy findings and/or signed informed consent form (ICF), the screening visit (Visit 1) will take place not more than 7 working days prior to randomization and the first dose administration (Visit 2). All patients will then visit the study clinic/investigational site after 7 (Visit 3), 14 (Visit 4) and 28 days (Visit 5) and at the End of Study/Early Termination visit (Visit 9). There are 3 weekly telephone visits after Visit 5. See Table 1.

4.2 Scientific Rationale for Study Design

This Phase 2 study is designed to provide data to support dose selection for Phase 3 based on a dose-response profile. The endoscopic healing rates for the different doses of X842 will be assessed after 4 weeks double-blind treatment. Endoscopy evaluation only at 4 weeks is based on the level and duration of acid control that can be achieved with X842. Symptom evaluation during the first 4 weeks will be assessed using the validated patient reported outcome (PRO) QOLRAD (Heartburn version) and patient diaries (RESQ-eDiary). Erosive esophagitis due to GERD is known as a chronic disease and the need for maintenance therapy is likely. To further understand the symptom pattern after 4 weeks of powerful gastric acid inhibition all patients undergoing endoscopy at 4 weeks, the end of blinded phase, will be administered 4 weeks treatment with lansoprazole 30 mg QD. Weekly and daily symptom evaluations will be done during this open-label treatment period to detect symptom pattern and symptom evaluation will be based on telephone interviews and patient diaries. Patients who will terminate the study prematurely will be scheduled for End of Study/Early Termination visit, 4 weeks after cessation of study treatment.

Evaluation of reflux related symptoms will be assessed by RESQ-eDiary, investigator's assessment and QOLRAD.

4.3 Justification for Dose

Four dose levels of X842 have been selected based on the results of three Phase 1 studies on X842 and previous development experience from its main metabolite linaprazan. PK/PD data has shown a close correlation between plasma concentrations of linaprazan and intragastric pH. The critical level of the plasma concentration of linaprazan after its C_{max} needed to ensure an intragastric pH > 4 has been identified to be approximately 240 nmol/L. In the first Phase 1 study the administration of 1 mg/kg X842 as a liquid formulation (mean absolute dose of 74 mg) resulted in a mean plasma linaprazan concentration of 225 nmol/L 12 hours after dose and this translated to a fall in intragastric pH to < 4 after this time point. This is similar to what was seen after healing dose of linaprazan at steady-state (K Andersson pers. com). A PK study (CX842A2102), on X842 50 mg QD dosing showed that the plasma concentration of linaprazan during 8 hours indicated good pH control, while the pH control was not maintained at 12, 22 and 24 hours. The plasma concentrations of linaprazan following 150 mg QD X842 indicated good pH control up to 12 hours, while concentration levels of linaprazan did not indicate maintained pH control at 22 and 24 hours after administration

The dose levels in this study (CX842A2201) are selected to accommodate for severe eGERD patients representing a "harder to treat" population. The Phase 1 PK/PD (intragastric pH over 48 hours) study (CX842A2103) on repeated BID dosing of 50 mg, 100 mg and 150 mg X842 during day 1 and 2 and once daily on day 3 showed a clear dose response. The 50 mg dose provided acid control (intragastric pH > 4) during 68% of time while the corresponding figure for the 150 mg dose was above 90% of time. In this study (CX842A2201), the lowest dose, 25 mg X842 BID is selected to provide a lower or similar pH control as seen during lansoprazole 30 mg QD at steady-state. The 25 mg dose of X842 should therefore provide healing rates that are lower or similar to what is seen after lansoprazole 30 mg QD. The highest dose 100 mg X842 BID is selected to provide intragastric pH control during 85% of the time. The intermediate X842 doses of 50 mg BID and 75 mg BID are selected to provide acid control of approximately 70-80% of the time. The predicted efficacy of the 75 mg and 100 mg doses of X842 are assumed to be superior to lansoprazole 30 mg QD, i.e., the recommended daily healing dose for patients with esophagitis.

4.4 End of Study Definition

All patients who participate in this study and complete Visit 9 (End of Study/Early Termination) visit are considered to have completed the study (Table 1).

The end of the study is defined as the date of the last visit of the last patient in the study.

5 Study Population

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, are not permitted.

The patients possibly eligible will be identified as the follows:

1. Patients identified during their routine endoscopy:
   - Patients must have erosive esophagitis identified during the routine endoscopy, before being considered for study screening (prior to signing the ICF).
   - This routine endoscopy will also serve as the index endoscopy in the study and the report should contain the endoscopy findings using the Los Angeles (LA) classification.
   - This routine endoscopy must be obtained within 7 working days of planned randomization, please refer to Inclusion criterion #4.
2. Patients invited for screening upper endoscopy based on their past medical history (both criteria must be met):
   a) LA grade C or D disease within the past 5 years before screening, demonstrated with endoscopy (endoscopy report issued by a gastroenterologist/endoscopist is accepted)
   b) In the Investigator's judgement the patient presents clear symptom relapse: patient may be treated with PPI, discontinued PPI treatment (patient's decision) or is being treatment naïve.

   For patients invited for screening upper endoscopy, the ICF will be signed prior to the endoscopy. The screening procedures must start with endoscopy and in case the patient doesn't show LA grade C or D erosions, the rest of the screening procedures must not be conducted. This screening endoscopy must be obtained within 7 working days of planned randomization.

The index/screening endoscopy video/digital image will be anonymized and saved for central storage. Imaging data must meet quality standards for adequate LA grading and must be accompanied by a report and videos/digital images to allow retrospective analysis of the endoscopy findings.

Investigators must keep a record of all screened patients even if they were not subsequently randomized in the study. This information is necessary to verify that patients were selected

without bias. The reason for screening failure should be stated for all patients screened but not randomized. The reason for withdrawal should be stated for all patients included but not completed study.

A screening number will be allocated to each patient in connection to the informed consent process at the screening visit. The screening number will allow identification of patients irrespective of their possible eligibility for the study.

For eligible patients, a randomization/treatment number will be assigned.

5.1 Inclusion Criteria

For inclusion in the study, patients must fulfill the following criteria:

1. Written informed consent must be obtained before any study related assessment is performed.
2. Male or female patient aged 18-75 years inclusive at the time of obtaining the informed consent.
3. Body mass index (BMI) ≥ 18 and ≤ 40 kg/m^2 at screening
4. Gastroesophageal reflux disease with endoscopically confirmed erosive esophagitis:
   - LA grade C or D ≤ 7 working days before randomization (with or without historical PPI treatment)
     or
   - LA grade A or B ≤ 7 working days before randomization

     and
     - history of treatment with standard healing course of PPI* for minimum of 8 weeks prior to screening and ≤ 7 working days of non-treatment during this period**.

     and
     - at least partial symptom response during the minimum of 8 weeks of PPI treatment.

     Note: Partial symptom response is defined as a clear symptom improvement (heartburn or regurgitation) after start of the PPI treatment course. To qualify, the patient's response must be YES to the Investigator´s standardized question to the patient: Did you feel a clear symptom improvement in heartburn or regurgitation after you started the PPI treatment course?

     * All PPIs EXCEPT lansoprazole

     ** Non-treatment days are counted from the last day of standard healing course of PPI therapy until endoscopy used for eligibility assessment demonstrating erosive esophagitis due to GERD."

5. Willing and able to comply with all aspects of the protocol (including PK sampling, capsule swallowing, diary completion, etc.)

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Female patients of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using one of the following adequate methods of contraception during dosing and for at least seven (7) days after the last dose of study medication:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking the first dose of study treatment. In case of oophorectomy alone, only when the reproductive status of the patient has been confirmed by follow-up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
   - Placement of a non-hormonal IUD
   - Double barrier methods of contraception: condom in combination with occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/vaginal suppository

   Note: Patients who are already on hormonal contraceptives prior to study enrollment must agree to:
   - replace hormonal contraception with double barrier method or
   - use double barrier contraception method in addition to the hormonal contraceptives
2. Female patients of non-childbearing potential not requiring a contraceptive method, are defined as
   - Pre-menopausal females with a documented tubal ligation or hysterectomy; or
   - Post-menopausal females defined as at least 12 months of amenorrhea (without an alternative medical cause) and confirmed with simultaneous serum follicle stimulation hormone (FSH), consistent with post-menopausal status according to central laboratory ranges.

   Patients who do not meet one of these two criteria above will be considered being of childbearing potential and are excluded unless using one of the adequate contraceptive methods defined in Exclusion Criterion #1.

3. Male patients with a partner of childbearing potential, unless they are willing to use condoms in combination with a second method of adequate contraception (e.g., double barrier method), and they agree not to father a child during dosing and for at least seven (7) days after the last dose of study medication. Each male patient will be considered as potent unless surgically sterilized (at least 6 months prior to screening).
4. History or presence of any clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disease or disorder which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the study results or the patient's ability to participate in the study
5. Patients with so-called "alarm features" in symptomatology, like odynophagia, severe dysphagia, bleeding, weight loss, anemia, and blood in stool pointing to a possible malignant disease of the gastrointestinal (GI) tract. Exclusion can be based on symptoms only.
6. Present clinically significant psychiatric diagnosis, at discretion of the Investigator
7. History of malignancy of any organ system (other than completely treated localized basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or in situ cervical carcinoma), within the past 5 years.
8. Presence of esophageal ulcer, stricture, Barrett´s esophagus or suspected esophagitis secondary to infection, inflammatory disease, ingestion of erosive chemicals or history of any surgical or medical condition which might significantly alter the GERD status or the absorption, distribution, metabolism or excretion of drugs. The Investigator is to be guided by evidence of any of the following: history of major gastrointestinal surgery such as gastrectomy, gastroenterostomy, bowel resection or transjugular intrahepatic portosystemic shunt (TIPS)
9. Known severe atrophic gastritis
10. Any planned major surgery within the duration of the study
11. Any clinically significant laboratory parameter outside reference value that, in the opinion of the Investigator, may suggest a new or insufficiently understood disease, may present an unreasonable risk to the patient as a result of his/her participation in the study, or may interfere with study assessments.

    Any of these screening laboratory tests results are exclusionary:

    - Serum ALT or AST > 1.5 × the upper limit of normal (ULN) for the central laboratory conducting the test
    - Serum Total Bilirubin > 1.5 × ULN for the central laboratory conducting the test
    - Serum Creatinine > 1.5 × ULN for the central laboratory conducting the test
    - Estimated glomerular filtration rate ≤ 59 mL/min (calculated using the Modification of Diet in Renal Disease equation)
12. History of a positive result for human immunodeficiency virus (HIV), Hepatitis B surface antigen (HBsAg), antibody to Hepatitis B core antigen (anti-HBcAg), or antibody to Hepatitis C virus (anti-HCV) or presence of these findings on screening

Note: Patients with positive anti-HBcAg along with negative HBsAg at screening will not be excluded IF they have a positive local anti-HBs test results not older than 6 months and active HBV infection has been ruled out by the Investigator.

13. After 10 min supine rest at the time of screening, any vital signs values outside the following ranges:
    - Systolic blood pressure (BP) > 160 mmHg or < 90 mmHg
    - Diastolic BP > 100 mmHg or < 60 mmHg
    - Heart rate < 40 or > 95 beats per min
14. History of long QTc syndrome (e.g., QTc ≥ 450 ms for males and ≥ 470 ms for females)
15. Cardiac arrhythmias or any clinically significant abnormalities in the resting 12-lead ECG at the time of screening, as judged by the Investigator
16. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to X842 or lansoprazole
17. Administration of another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment with less than one month between administration of last dose and first dose of IMP in this study.
18. Positive screen for drugs of abuse at screening (for the list of drugs for testing please refer to the laboratory manual).
19. Current or history of alcohol, drug abuse and/or use of anabolic steroids within 2 years prior to screening
20. Women who are pregnant or breast feeding.
21. Patient is an employee of the Investigator or study site, with direct involvement in the proposed study or other studies under the direction of that Investigator or study site, as well as family members of the employees or the Investigator.
22. Patients who have previously participated (completed or withdrawn) in this study CX842A2201

5.3 Lifestyle Considerations

The patients must be willing to comply to the following restrictions during the entire study duration, i.e., from screening to the End of Study/Early Termination visit.

5.3.1 General Restrictions

- Contraception requirements: Women of childbearing potential and male patients with a partner of childbearing potential are expected to use adequate methods of contraception during dosing of study medication and for at least seven (7) days after the last dose of study medication (see Exclusion Criteria 1 and 3, Section 5.2).

- Activity: Study patients must refrain from strenuous exercise (defined as greater than 70% of the maximal pulse rate for 1 hour or more) for 72 hours before each blood collection for clinical laboratory tests (except screening).
- Blood donation: The patients must not donate blood or plasma during the study participation
- Participation in other clinical studies: Study patients are not allowed to participate in any other clinical study during the study period.

5.3.2 Prior and Concomitant Medication and Therapy/Procedures

The patients are not allowed to concomitantly use any medication or therapy during the study likely to influence the outcome of this clinical trial. This includes:

- Agents affecting digestive organs
    - PPIs (e.g., omeprazole, pantoprazole, lansoprazole (except study medication), rabeprazole, esomeprazole, dexlansoprazole, dexrabeprazole, vonoprazan, etc.),
    - H_2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine, niperotidine, roxatidine, lafutidine, ebrotidine, etc.),
    - muscarinic receptor 3 antagonists (e.g., atropine, scopolamine, hyoscyamin, ipratropium, tiotropium, pirenzepine, darifenacin, oxybutinin, revefenacin, etc.),
    - gastrointestinal prokinetic agents (e.g., metoclopramide, cisapride, domperidone, bromopride, alizapride, clebopride, itopride, cinitapride, mosapride, etc.),
    - anti-cholinergic agents (e.g., pirenzepine, telenzepine),
    - prostaglandins (e.g., misoprostol, enprostil, etc.),
    - antacids,
    - anti-gastrin agents (e.g., proglumide, oxethazaine, etc.).
- Medications that may affect the metabolism of X842 or linaprazan (cytochrome P450 [CYP] inhibitors and inducers) and medications that may be affected by X842 or linaprazan (substrates of CYP enzymes and drug transporters). For a comprehensive list, see Section 10.9 (Appendix 9),
- Medications contraindicated for use in combination with lansoprazole,
- Medications with reported drug–drug interactions with lansoprazole (warfarin, clopidogrel, ketoconazole, itraconazole, digoxin, tacrolimus, theophylline, methotrexate) and
- *H. pylori* eradication therapy (antibiotics along with PPI).

Patients are not permitted to undergo surgical intervention (e.g., fundoplication) for reflux disease or other antireflux procedures during study participation. Any planned major surgery within the duration of the study is exclusionary.

5.4 Screen Failures

Screening failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized/entered into the study. A minimal set of screening failure information is required to ensure transparent reporting of screening failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria and any SAE.

Patients who do not meet the criteria for participation in this study may be rescreened once. If the re-screening occurs less than 3 months after the first screening visit, serology tests do not need to be repeated.

6 Study Drug

Study drug is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study patient according to the study protocol.

6.1 Study Drugs Administered

Study Drug Name:	X842	X842 Dummy	Lansoprazole	Lansoprazole Dummy
Dosage Formulation:	Immediate release tablet	Tablet	Capsule	Capsule
Unit Dose Strength(s)/Dosage Level(s):	X842 25 or 50 mg	Placebo for X842	Lansoprazole 30 mg	Placebo for lansoprazole
Route of Administration:	Oral	Oral	Oral	Oral
Dosing Instructions:	**4-week double-blind treatment** X842 25 mg BID 2 tablets (X842 25mg + X842 dummy) and 1 capsule (lansoprazole dummy) in the morning, and 2 tablets (X842 25 mg + X842 dummy) in the evening. X842 50 mg BID 2 tablets (X842 50 mg + X842 dummy) and 1 capsule (lansoprazole dummy) in the morning, and 2 tablets (X842 50 mg + X842 dummy) in the evening. X842 75 mg BID 2 tablets (X842 50 mg + X842 25 mg) and 1 capsule (lansoprazole dummy) in the morning, and 2 tablets (X842 50 mg + X842 25 mg) in the evening. X842 100 mg BID 2 tablets (X842 50 mg×2) and 1 capsule (lansoprazole dummy) in the morning, and 2 tablets (X842 50 mg×2) in the evening. Lansoprazole 30 mg QD 2 tablets (X842 dummy×2) and 1 capsule (lansoprazole 30 mg) in the morning, and 2 tablets (X842 dummy×2) in the evening.			
	4-week lansoprazole 30 mg QD For all patients continuing on open-label phase: lansoprazole 30 mg 1 capsule in the morning.			
Packaging and Labeling:	Study drug will be provided in blister pack. Each blister pack will be labeled as required per country requirement.	Study drug will be provided in blister pack. Each blister pack will be labeled as required per country requirement.	Study drug will be provided in blister pack. Each blister pack will be labeled as required per country requirement.	Study drug will be provided in blister pack. Each blister pack will be labeled as required per country requirement.

6.2 Preparation/Handling/Storage/Accountability

The blister packs containing the study medication will be dispensed as per randomization schedule by a site pharmacist or a registered nurse under supervision of other site personnel.

The Investigator will maintain a Drug Dispensing Log detailing the dates and quantities of study medication received, dispensed to and used by each patient and study medication returned or destroyed at the end of the study. Any discrepancies between dispensed and returned study drug must be explained and documented. Products deliberately and/or accidentally destroyed by the Investigator/pharmacy or the patient, must be accounted for. Patients will receive one additional blister pack at Visit 2/Day 0 to keep overage in case they return within the allowed visit window. Patients should return this additional blister pack for accountability at every visit and returned on Visit 5.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

Patients will be randomized to receive either one of the four doses of the test product (48 patients per dose group) or the reference product lansoprazole (48 patients).

The randomization list will be generated, and the original randomization list will be kept.

All patients will be centrally randomized using an Interactive Voice Response System (IVRS). Each patient will be assigned a unique number (randomization number) that encodes the patient's assignment to one of the five arms of the study, according to the randomization schedule generated by Parexel using a validated computer program. Details of the procedure are described in the IVRS Manual provided to all clinic/investigational sites.

Randomization will be set as approximately 50% of patients with LA grade A or B and approximately 50% of patients with LA grade C or D.

6.3.2 Blinding

This is a double-blind study and the allocation of treatments will not be disclosed until the file has been declared clean and the database has been locked.

The IMP tablets will be identical in appearance (dummy, 25 mg and 50 mg tablets) and lansoprazole, the reference treatment (capsule), will be identical in appearance as its dummy. All efforts will be made at the clinic/investigational site to maintain the blind. All study medication will be provided in blister packs according to the randomization list through IVRS.

6.3.3 Emergency Unblinding During the Study

The treatment code may only be broken by the Investigator in case of emergency when knowledge of the treatment received is necessary for the proper medical management of the patient.

In case of emergency the Investigator may contact the Sponsor's Medical Monitor for drug specific input prior to disclosure of the treatment allocation. However, the Investigator will make the decision to unblind the treatment assignment.

For unblinding procedures in case of a potential suspected unexpected serious adverse reaction (SUSAR), refer to Section 8.4.6.1.

6.4 Study Drug Compliance

The first administration will take place as early as possible after randomization until 2 pm on Day 0, or at 8 pm on Day 0. Diary cards will be handed out together with the study drug to the patients and they will be instructed to document date and time of the following administrations on the diary card. The patients will bring the diary card at each visit to the study clinic/investigational site. In addition, the patients will also bring the remaining capsules and tablets for reconciliation. Treatment compliance will be based on the number of remaining capsules and tablets.

6.5 Return and Destruction of Investigational Medicinal Products

Any unused study medication will be returned to the Sponsor and/or CRO for destruction. Used/unused blisters will be destroyed at the study sites after reconciliation by the Clinical Research Associate (CRA). The CRA will perform final study drug accountability reconciliation at the study end to verify that all unused study drug is adequately destroyed/returned and documented.

6.6 Prior and Concomitant Therapy

The patients are not allowed to concomitantly use any medication or therapy likely to influence the outcome of this clinical trial. This includes: agents affecting digestive organs (PPIs, H_2 receptor antagonists, muscarinic receptor 3 antagonists, gastrointestinal prokinetic agents, anti-cholinergic agents, prostaglandins, antacids, anti-gastrin agents), medications involved in the metabolism of X842 and linaprazan (CYP substrates, inhibitors, inducers and transporter inhibitors, as specified in Appendix 9), medications contraindicated for use in combination with

lansoprazole, medications with reported drug–drug interactions with lansoprazole (warfarin and clopidogrel) and *H. pylori* eradication therapy.

For list of medication or therapy that are not allowed concomitantly, see Section 5.3.2. Other concomitant medications that the patient receives on a regular basis may continue, if in the opinion of the Investigator, it does not put the patient at undue risk or does not interfere with the study evaluations.

Any change in concomitant medication during the course of the study will be recorded by the Investigator in the relevant section of the case report form (CRF).

6.6.1 Rescue Medication

All restrictions regarding the use of medications or therapies which are likely to influence study outcome are applicable for the entire duration of the study (please refer to Section 5.3.2 for not permitted medications).

6.7 Dose Modification

Dose modification for an individual patient is not allowed.

6.8 Intervention After the End of the Study

There will be no treatment with X842 or lansoprazole available, provided by Sponsor, after End of Study participation. Following discontinuation of study treatment some patients may need additional therapy for their erosive esophagitis due to GERD. The Investigator should ensure patients re-establish care with a physician during the open-label treatment period in order to avoid a lapse.

7 Discontinuation of Study Drug and Patient Discontinuation

7.1 General Withdrawal Criteria

Patients are free to discontinue their participation in the study at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care. If possible, the reason for withdrawal of consent should be documented.

Patients may be discontinued from the study at any time at the discretion of the Investigator for any of the following reasons:

- Severe non-compliance to study protocol procedures, as judged by the Investigator and/or Sponsor

- Significant AEs posing a risk for the patient, as judged by the Investigator and/or Sponsor
- Withdrawal of informed consent by the patient. If consent is withdrawn, the patient will not receive any further study treatment or further study observation. Note that the patient may need to undergo additional tests to withdraw safely
- Withdrawal of informed consent by the patient to the use of biological samples as judged by the Investigator and/or Sponsor
- At the discretion of the Investigator, when he/she believes continued participation is not in the best interest of the patient
- Positive pregnancy test (Pregnant women should be followed until delivery as described in Section 8.4.8)
- Severe laboratory abnormalities (please refer to Treatment and follow-up of AEs in Section 8.4.7):
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 x upper limit of normal (ULN)
    - AST or ALT > 5 x ULN (for more than 2 weeks)
    - ALT or AST > 3 x ULN with total bilirubin (TBL) > 2 x ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome) or with international normalized ratio (INR) > 1.5
    - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Diagnosis of a malignancy during study (excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin).
- The Sponsor or a Regulatory Agency requests withdrawal of the patient.

7.2 Procedures for Discontinuation of a Patient from the Study

A patient who prematurely discontinues participation in the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen by the Investigator and assessed according to the procedures scheduled for the End of Study/Early Termination visit. Any ongoing AEs will be followed as described in Section 8.4.7.

7.3 Patient Replacement

Patient replacement is not planned.

7.4 Loss of Patients to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the clinic/investigational site until and including Visit 9/End of Study/Early Termination visit.

The following actions must be taken if a patient fails to return to the clinic for a required study visit or fails to be available for a telephone visit:

- The clinic/investigational site must attempt to contact the patient and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient missed one or more visits, the Investigator or Designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). The last attempt to contact the patient must be at the time for Visit 9. These contact attempts should be documented in the patient's medical record.

8 Study Assessments and Procedures

The study assessments are described in the sections below and the timing of these assessments are detailed in the SoA table (see Table 1).

The Principal Investigator will provide the Sponsor/Designee with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor/Designee in the electronic CRF (eCRF) and in all required reports.

It is important that PK blood sampling occurs as close as possible to scheduled time and is always accompanied with the time for the latest study medication tablet administration. In order to achieve this, the preferred timing priority order at a particular time point is:

- QOLRAD completion
- Blood samples for PK
- Safety laboratory samples
- ECG, vital signs, physical examination
- Investigator assessment
- Study drug administration

The actual sampling time and the time for the latest study medication tablet administration should always be recorded in the eCRF and will be used in the calculation of the PK parameters.

Blood samples will be drawn by venipuncture or an indwelling venous catheter at time-points specified in the detailed schedule of events in SoA (Table 1).

Detailed instructions for collection of samples will be provided in the laboratory manual.

The maximum volume of blood samples (safety samples and PK samples) collected during the study from each patient, including extra assessments that may be required, will not exceed 450 mL (i.e., less than the volume drawn during a regular blood donation).

8.1 Demographics and Other Baseline Characteristics

8.1.1 Informed Consent

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 10.1.3.

8.1.2 Eligibility Criteria

Eligibility criteria should be checked during screening period and confirmed prior to inclusion/randomization. The criteria are specified in Sections 5.1 and 5.2.

8.1.3 Demographic Information

The following demographic data will be recorded: gender, age, and ethnic origin.

8.1.4 Weight and Height

Weight and height will be measured wearing light clothes and without shoes. Body mass index (BMI) will be calculated from the height and weight recorded and rounded off to the nearest whole number.

The body weight recorded at screening will be used for determination of eligibility and the body weight recorded at baseline, after the 4-week double-blind period and at the End of Study is a safety assessment. The method of weight assessment should be the same across all visits.

8.1.5 Medical/Surgical History

Medical/surgical history will be obtained by patient interview in order to verify that the eligibility criteria are met.

Medical history includes recent medical history, previous medical history (only significant medical or surgical illness), smoking, alcohol and intake of drugs of abuse and/or anabolic steroids.

8.1.6 Prior and Concomitant Medication

Prior medication will be obtained by patient interview in order to verify that the eligibility criteria are met (see also Section 5.3.2).

Medications are classified as prior if the stop date was before or on the day of the first dose administration (pre-dose) and as concomitant if ongoing on the day of the first dose administration, stopped after the first dose administration or started after the first dose administration.

Any use of concomitant medication from screening until the End of Study/Early Termination visit must be documented appropriately in the patient's eCRF. Relevant information (i.e., name of medication, total daily dose, unit, start and stop dates, reason for use if consistent with the definition of an AE) must be recorded. All changes in medication should be noted in the eCRF.

8.1.7 Serology (HIV and Hepatitis B/C Virus) Testing

Patients will be tested for HIV and hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBcAg), antibody to hepatitis C virus (anti-HCV at central lab) prior to inclusion/randomization into the study in order to assess eligibility and protect personnel handling the blood samples.

8.1.8 Pregnancy Test

All women of childbearing potential will undergo a serum pregnancy test at screening and a urine pregnancy test (dipstick) prior to administration of study drug dose at Visit 5, and at End of Study/Early Termination.

8.1.9 Urine Drug Screen

Urine will be screened for drugs of abuse at screening using local drug screen tests (see the laboratory manual). Additional random tests can be performed during the study period.

8.2 Efficacy Assessments

Upper endoscopy for the examination of esophagus will be used to confirm patient eligibility as well as the confirmation of the primary endpoint. Imaging data must meet quality standards for adequate LA grading and must be accompanied by a report and videos/digital images to allow retrospective analysis of the endoscopy findings. The endoscopy has to be performed by an experienced endoscopist. The patient has to be fasting prior to endoscopy, i.e., drinking, eating, and smoking are not allowed from midnight prior to the assessment. The index/screening endoscopy must be taken within seven (7) days of the planned treatment day. Endoscopies taken prior to informed consent signatures can be used once the patient agrees to participate in the study and signs the informed consent. The endoscopy examinations must be recorded on a video

shot/digital images. The length, views and other technical specifications of the videos/digital images are described in the Image Acquisition Guidelines, separate document.

The endoscopy videos/digital images will be evaluated by Investigator or endoscopy specialist, as required. Grade of erosive esophagitis due to GERD will be determined by the appropriately trained Investigator or endoscopist according to the LA classification (see Appendix 8). The LA grading of the erosive esophagitis due to GERD should be documented in the endoscopy report.

The endoscopy videos/digital images will be collected into a central database, with the appropriate anonymization. All videos and digital images will be centrally reviewed retrospectively. This review will include reassessment of the LA grading and other findings which may constitute exclusion criterion. The central reading evaluation will override the investigators evaluations. Data obtained from patients deemed to have been ineligible for study enrollment following the retrospective analysis will be excluded from the per protocol analysis.

8.3 Safety Assessments

8.3.1 Physical Examinations

A complete physical examination will be performed as designated on the SoA and will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular system, abdomen (including liver and spleen), lymph nodes, genitourinary system (optional) and extremities (musculoskeletal system).

8.3.2 Weight and BMI

Weight will be measured wearing light clothes and without shoes as designated on the SoA. The method of weight assessment will be the same across all visits. Body mass index (BMI) unit is kg/m^2 and calculated as weight in kg and height in meter.

8.3.3 Vital Signs

Examination of vital signs will be performed as designated on the SoA. Systolic and diastolic BP and heart rate (pulse) will be measured in supine position after 10 min of rest. Body temperature and respiratory rate will be measured pre-dose.

8.3.4 Resting 12-lead Electrocardiograms

Single 12-lead ECG will be recorded as designated on the SoA in supine position after 10 min of rest using an ECG machine. Heart rate and PQ/PR, QRS, QT and QTcF intervals will be recorded. Safety ECGs will be reviewed and interpreted on-site by the Investigator.

Abnormalities in an ECG will be assessed as "clinically significant" or "not clinically significant." An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 8.4).

8.3.5 Clinical Safety Laboratory Assessments

Blood samples for analysis of clinical chemistry, hematology and coagulation parameters will be collected through venipuncture or an indwelling venous catheter and sent to the certified clinical chemistry laboratory and analyzed by routine analytical methods. Urine laboratory analysis will be performed at the research clinic/investigational site using dip sticks. Additionally, local testing at site includes urine drug abuse test and urine pregnancy test (dipstick) will be performed. For details, see the laboratory manual.

The following safety laboratory parameters will be assessed at time-points defined in SoA (Table 1):

Clinical Chemistry	**Hematology**
Alanine aminotransferase (ALAT)	Hematocrit
Alkaline phosphatase (ALP)	Hemoglobin (Hb)
Albumin	Platelet count
Aspartate aminotransferase (ASAT)	Red blood cell (RBC) count
Bilirubin (total and conjugated)	White blood cell (WBC) count with differential count
Calcium	
Chloride	**Coagulation**
Creatinine	International Normalized Ratio
Gamma-glutamyl transferase (GGT)	
Magnesium	
Phosphorous	**Urinalysis (dip stick)**
Potassium	Glucose
Sodium	Hemoglobin/erythrocytes
Urea nitrogen	Nitrite
Uric acid	Protein
Gastrin	Specific gravity
	pH
	Ketones
Viral serology	**Other**
Hepatitis B (HBsAg)	Urine pregnancy test (HCG)[1]
Anti-hepatitis B core antigen (Anti-HBcAg)	Follicle stimulating hormone (FSH)[2]

Hepatitis C antibody (anti-HCV) Human immunodeficiency virus (HIV-1 and -2)	Urine drug abuse screen[3] *H. pylori*[4]

[1] Women of childbearing potential only (local urine test at site)
[2] At screening, post-menopausal women only, as applicable (central laboratory)
[3] At screening, local urine sample at site
[4] *H. pylori* result will not be needed for randomization (central laboratory)

8.3.6 Concomitant Medication

Prior medication will be obtained by patient interview in order to verify that the eligibility criteria are met (see also Section 6.6).

Medications are classified as prior if the stop date was before or on the day of the first dose administration (pre-dose), and as concomitant if ongoing on the day of the first dose administration, stopped after the first dose administration or started after the first dose administration.

8.3.7 Reflux Related Symptoms Assessed Based on PRO

Reflux related symptoms will be assessed based on QOLRAD, which is a PRO developed by Wiklund et al in 1998 [8]. It has been translated and evaluated in multiple languages. The heartburn version of the QOLRAD is a disease specific instrument and contains 25 questions addressing concerns associated with gastrointestinal symptoms. The questions are rated on a seven-grade Likert scale; the lower the value, the more severe the impact on daily functions. The questions are categorized into five domains: emotional distress (six questions), sleep disturbance (five questions), vitality (three questions), food/drink problems (six questions) and physical/social functioning (five questions). It will be assessed at baseline, week 1, 2, and 4 (see Table 1). The QOLRAD will be completed pre-dose by patients at Visits 2, 3, 4, 5, and 9 (please refer to SoA).

Reflux related symptoms will be also assessed based on a modified RESQ-eDiary; an electronic symptom diary developed for use in partial responders to PPI. RESQ-eD has three Domains (i.e. Heartburn, Other GERD signs/symptoms and Regurgitations/Reflux) and eight Items. Patients will be asked to report every 12-hours, once before the morning dose and once before the evening dose of the IMP.

8.3.8 Reflux Related Symptoms Assessed by Investigator

Symptoms of GERD may include: heartburn (defined as a retrosternal burning pain rising from the epigastrium which may radiate into the pharynx), acid regurgitation (upward flow of sour

fluid toward the mouth), dysphagia, epigastric pain/discomfort, retrosternal tightness, burping/belching, nausea/vomiting, fullness, lower abdominal pain, flatulence, coughing.

At each visit, Investigator will assess the severity of patients' heartburn, regurgitation and dysphagia in the 7 days prior to the visit. The assessment will include both the severity grade and the frequency of symptoms. Assessments will be captured in EDC.

The potential frequency is defined as 7-graded Likert scale:

- All of the time;
- Most of the time;
- Quite a lot of the time;
- Some of the time;
- A little of the time;
- Hardly any of the time;
- None of the time.

Symptoms are scored as follows:

- none (no complaints),
- mild (aware of symptom, but easily tolerated),
- moderate (discomforting symptom, sufficient to cause interference with normal daily activities and/or sleep),
- severe (incapacitating symptom, with inability to perform normal daily activities and/or sleep).

8.3.9 Pharmacokinetic Samples and Analysis

Venous blood samples (approximately 5 mL, exact details are provided in the laboratory manual) for the determination of plasma concentrations of linaprazan and X842 after administration of the study drug, will be collected at the pre-specified time-points (see Table 1).

The date and time of collection of each sample and the time for the latest study drug administration will be recorded in the eCRF. PK samples will be collected 12 hours after the previous study drug dose administration or as close to this timepoint as possible, but always pre-dose (close before the first and the second dose administration at Days 7, 14 and 28).

Plasma samples for determination of plasma concentrations of linaprazan and X842 will be analyzed by means of a validated LC-MS/MS method (see the laboratory manual). The details of

the analytical method used will be described in a separate bioanalytical report. Detailed instructions for collection, handling, labeling, storage and shipment of samples will be provided in the laboratory manual.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definitions

8.4.1.1 Adverse event

An AE is any untoward medical occurrence in a clinical study patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal values from relevant tests, such as clinical safety laboratory tests, ECGs, vital signs), symptom, or disease temporally associated with the use of an IMP, regardless of whether it is considered related to the IMP.

A TEAE is any AE only present after the initiation of IMP administration or any event already present that worsens in either intensity or frequency following exposure to the IMP.

Collection of AEs will start directly after the ICF has been signed. Only AEs related to study procedure will be collected between screening visit and the first IMP administration.

8.4.1.2 Serious adverse event

An SAE is any AE that:

- results in death
- is life-threatening (this refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent any of the SAEs defined above)

Examples of medically important events are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalization, development of drug dependency, and drug abuse.

Hospitalization is defined as any inpatient admission usually involving at least an overnight stay.

Planned hospitalizations or surgical interventions for a condition that existed before the patient signed the ICF and that did not change in intensity are not SAEs.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

8.4.1.3 Adverse events of special interest (AESI)

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

All AESI, serious and non-serious, **must be reported within 24 hours** of identification using the same reporting process as for SAE reporting.

The following conditions should be considered AEs of special interest and require expedited reporting:

a. ALT or AST ≥ 8 x ULN
b. ALT or AST ≥ 5 x ULN for 2 or more weeks
c. ALT or AST ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN (or ALT or AST ≥ 3 x ULN **and** INR > 1.5)
d. ALT or AST ≥ 3 x ULN accompanied by clinical symptoms believed to be related to hepatitis or hypersensitivity, such as new or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash
e. ALT or AST ≥ 5 x ULN but < 8 x ULN and cannot be monitored at least weekly for ≥ 2 week

Hy's Law, defined as ≥ 3 x ULN ALT or AST **with coexisting** ≥ 2 x ULN total bilirubin with no alternative explanation for the biochemical abnormality other than IMP (for example elevated ALP indicating cholestasis, viral hepatitis, other medication) must always be reported without delay as an AESI, and, if applicable, also as an SAE.

All potential drug-induced liver injuries (PDILI) events require immediate action, testing, and monitoring. If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible.

PDILI events require notification of the Medical Monitor within 24 hours (e.g., by laboratory alert), and the patient must be discussed with the Medical Monitor as soon as possible. Patients with PDILI must be assessed to determine if the study drug must be discontinued (please refer to General withdrawal criteria, Section 7.1).

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Every liver laboratory trigger or liver event as defined in Table 2 should be followed up by the Investigator or designated personnel at the trial site as summarized below (please also refer to General withdrawal criteria, Section 7.1).

A. Liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation. The repeat assessment can be done as an unscheduled study visit or at a local laboratory. In this case, local laboratory normal ranges should be recorded, and the results should be made available to the trial investigator immediately, and the data recorded on the CRF.
- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

B. Liver event:

- Repeating the LFT as soon as possible to confirm elevation as appropriate
- Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline value
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist’s consultancy, based on investigator’s discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

Table 2 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
A. LIVER LABORATORY TRIGGERS	**ALT or AST > 3 × ULN, but ALT and AST ≤ 5 × ULN** **TBL > 1.5 × ULN, but TBL≤ 2 × ULN**
B. LIVER EVENTS	
Laboratory events (any of the listed criteria)	**ALT or AST > 5 × ULN** **ALP > 5 × ULN** **TBL > 2 × ULN (in the absence of known Gilbert syndrome)** **Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)**
Adverse events (any of the listed criteria)	**Any clinical event of jaundice (or equivalent term)** **ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia** **Any adverse event potentially indicative of a liver toxicity ***

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

It is the responsibility of the Investigator to follow up on all SAEs until the patient has recovered, stabilized, or recovered with sequelae, and to report to the Sponsor or Designee all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

Serious adverse events spontaneously reported by a patient to the Investigator within 30 days after the last follow-up assessment must be handled in the same manner as SAEs occurring during the study. These SAEs will be reported to the Sponsor or Designee.

8.4.1.4 Serious adverse drug reaction

The term serious adverse drug reaction (SADR) is to be used whenever either the Investigator or Sponsor or designee assessed the SAE as possibly or probably related to the IMP.

8.4.1.5 Suspected unexpected serious adverse reaction

A SUSAR is any SADR whose nature or intensity is not consistent with the current version of the IB (unexpected).

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

Collection of AEs will start directly after the ICF has been signed. During the screening period, only AEs related to study procedure will be reported. All AEs (including SAEs) will be collected until the End of Study/Early Termination visit. Any AE with start date on the day or after the IMP administration must be recorded with start time. At the follow-up visit, information on new AEs or SAEs, if any, and stop dates for AEs recorded and ongoing during the dosing period must be recorded. Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded in the Medical History Log of the eCRF, not in the AE Log.

Investigators are not obligated to actively seek new AE or SAE after conclusion of the study participation (for follow-up of AEs please refer to Section 8.4.7). However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor or Designee.

8.4.3 Assessment of Severity/Intensity

The grading of the severity/intensity of AEs will follow the common terminology criteria for AEs (CTCAE) v4.03 [9]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the severity/intensity of an AE using the following definitions, and record it on the AE Form in the CRF:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self- care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Note: a semi-colon indicates 'or' within the description of the grade.

8.4.3.1 Assessment of causal relationship

The Investigator must assess the causal relationship between an AE and the IMP using the definitions below and record it the AE Log of the eCRF:

- Probable – the AE has a strong temporal relationship to the IMP or recurs on re-challenge, and another etiology is unlikely or significantly less likely
- Possible – the AE has a suggestive temporal relationship to the IMP, and an alternative etiology is equally or less likely
- Unlikely – the AE has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the AE)

An AE is considered causally related to the use of the IMP when the causality assessment is probable or possible.

8.4.3.2 Assessment of outcome

The Investigator must assess the outcome of an AE using the definitions below and record it on the AE Log of the eCRF:

- Recovered – the patient has recovered completely, and no symptoms remain
- Recovering – the patient's condition is improving, but symptoms still remain
- Recovered with sequelae – the patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally, but has some motor impairment)
- Not recovered – the patient's condition has not improved, and the symptoms are unchanged (for example, an atrial fibrillation has become chronic)
- Death

8.4.4 Collecting Adverse Events

In general, abnormal findings at screening should be recorded in the patient's Medical History.

Adverse events identified using any of the following methods will be recorded:

- AEs spontaneously reported by the patient
- AEs observed by the Investigator or medical personnel

- AEs elicited based on non-leading questions from the Investigator or medical personnel

8.4.5 Recording Adverse Events

Adverse events must be recorded in the AE Log of the eCRF. The Investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms; start and stop dates, start and stop time; intensity; causal relationship to IMP; action taken, and outcome. If the AE is serious, this must be indicated in the eCRF.

Adverse events, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

If the severity/intensity of an AE increases a new AE Form must be completed in the eCRF.

Adverse events must be documented in clear, unambiguous medical language, without use of abbreviations or acronyms.

8.4.6 Reporting of Serious Adverse Events

On discovery, all SAE/AESIs should be immediately reported (latest within 24 hours of knowledge of the event) to Parexel Safety Services by:

Entering the AE in the appropriate section (AE page and/or SAE page) of the eCRF, indicating that the event is considered serious, and providing all the details per the eCRF completion guidelines

and

Completing the SAE report form and e-mailing/faxing the documents to Parexel Safety Services as per details below:

France (Paris) Mailbox: 249403_Safety@parexel.com
France (Paris) Fax numbers: +33 1 44 90 32 75 or +33 1 44 90 35 34

In the event that the site is unable to complete the SAE form or eCRF entry to report the event within 24 hours of their knowledge of the event, the Investigators may report the SAE over the telephone via the SAE answering service, and then provide the completed SAE form via **(fax or email)**, or complete the eCRF entry of the event (within the next 24 hours). If questions arise regarding the reporting procedures or the specifics of the reporting of an event, sites may call (English) utilizing the following numbers:

Paris: +33 1 44 90 32 90

In case the eCRF cannot be accessed, the SAE should be reported by manually completing the paper SAE Form, provided in the investigator site file (ISF).

The SAE report is reviewed by a designated person at Parexel to ensure that the report is valid and correct. For fatal or life-threatening SAEs where important or relevant information is missing, immediate follow-up is undertaken and queries to the site are raised by Parexel. Investigators or other site personnel should inform designated person of any follow-up information on a previously reported SAE immediately but no later than the end of the next business day of when he/she becomes aware of it.

If an SAE report is updated, the designated study personnel will be informed.

If any additional documentation is required (e.g., hospital discharge letter, autopsy report, etc.), designated person will request this information from the study site.

The study site should notify the CRA via phone or e-mail about the submission of the SAE report. As soon as the site personnel have access to the eCRF, the SAE should be reported electronically as well.

The Sponsor or Designee will assume responsibility for reporting SAEs to competent authorities (CAs) and the independent ethics committees (IECs) in accordance with local regulations.

8.4.6.1 Reporting of SUSARs to EudraVigilance, local CA and IEC

The term SADR is used whenever either the Investigator or Medical Monitor deems a blinded SAE as possibly or probably related to IMP. If a SADR is assessed as unexpected by the Medical Monitor, it is a potential SUSAR.

Under such circumstances, the Sponsor Medical Monitor will be unblinded (see Global Safety Reporting Procedure) and reported to the CAs (via the EudraVigilance database, where applicable), and to the IEC, in accordance with local regulations and applicable standard operating procedures (SOPs) within the following timelines:

- 7 calendar days if fatal or life-threatening (follow-up information within an additional 8 days)
- 15 calendar days if non-fatal and non-life-threatening (for initial and follow-up information)

The clock for expedited initial reporting (Day 0) starts as soon as the Sponsor or Designee has received the information containing the minimum reporting criteria. The date should be documented on an acknowledgment receipt.

The Medical Monitor is responsible for medical review of the SAE narrative in the Council for International Organizations of Medical Sciences for (or equivalent) prior to expedited reporting.

The Sponsor or Designee is responsible for informing the Investigators concerned of relevant information about potential SUSARs (blinded data) that could adversely affect the safety of patients.

The Sponsor or Designee is responsible for once a year throughout the clinical study (or on request), to submit a safety report to the CA and the IEC taking into account all new available safety information received during the reporting period.

8.4.7 Treatment and Follow-up of Adverse Events

Patients with AEs that occur during the study must be treated according to daily clinical practice at the discretion of the Investigator. Adverse events must be followed up until resolution or until End of Study/Early Termination visit, whichever comes first. At the follow-up visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded. Adverse events assessed as stable by the Investigator at the End of Study/Early Termination visit will not have to be followed up until resolution.

For the treatment and follow-up of AESIs please refer to Section 8.4.1.3.

All SAEs not resolved by the end of the study or that have not resolved upon the patient's discontinuation in the study must be followed until the event resolves, the event stabilizes, or the event returns to baseline if a baseline value is available.

8.4.8 Pregnancy

In case of pregnancy or suspicion of possible pregnancy, the study treatment must be stopped immediately, and the patient discontinued from participation in the study. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of the contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the patient was discontinued from the study.

All events of congenital abnormalities/birth defects are SAEs. Pregnancy complications or spontaneous miscarriages should also be reported and handled as AEs or SAEs. All outcomes of pregnancy must be reported to the Sponsor or Designee by the Principal Investigator on the pregnancy outcomes report form. Follow-up must be performed until delivery or pregnancy termination.

The Investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study, and report to Sponsor or Designee. The partner will also be followed to determine the outcome of the pregnancy.

Any pregnancy that occurs during study participation must be reported to the Sponsor or Designee on the pregnancy form, immediately or within 24 hours of the Investigator learning of its occurrence.

8.5 Treatment of Overdose

An overdose is a dose in excess of the dose specified for each cohort in this clinical study protocol (CSP).

There are no data on overdosing of X842. There is no known antidote and an overdose in a study patient should be monitored closely and treated symptomatically. The IMP X842 is a glutaric acid prodrug of linaprazan that has been extensively studied by AstraZeneca in more than 2000 patients and 400 healthy subjects. Based on published data, linaprazan was safe and well tolerated, [6, IB].

There is limited data available regarding the effects of overdose of lansoprazole in humans. However, daily doses of up to 180 mg of lansoprazole orally and up to 90 mg of lansoprazole intravenously have been administered in trials without significant undesirable effects. In one reported overdose, a patient consumed 600 mg of lansoprazole (Prevacid) with no adverse reaction. Oral lansoprazole doses up to 5000 mg/kg in rats [approximately 1300 times the 30 mg human dose based on body surface area (BSA)] and in mice (about 675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs [11].

In the case of suspected overdose, the patient should be monitored. Lansoprazole is not significantly eliminated by hemodialysis. If necessary, gastric emptying, charcoal and symptomatic therapy is recommended [12].

An overdose should be documented as follows:

- An overdose with associated AE is recorded as the AE diagnosis/symptoms in the AE Log of the eCRF.
- An overdose without associated symptoms is only reported in the patient's medical records.

8.6 Handling, Storage and Destruction of Laboratory Samples

All biological samples will be handled according to local regulations.

The biological samples will be labeled with a unique code and be stored under Cinclus's control for a maximum of 15 years (some samples may be stored for much less time) to analyse metabolites of X842, analyse associated medicines and explore or validate biomarkers/assays/new techniques to help develop ways to detect, monitor or treat reflux disease and other gastric acid related diseases e.g., peptic ulcer disease, *H. pylori* infection.

8.7 Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The study site should keep full traceability of collected biological samples from the patients while in storage at the study site until shipment and keeps documentation of receipt of arrival.

The sample receiver (the analytical laboratory) keeps full traceability of the samples while in their storage and during use until used or disposed of.

The Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

8.8 Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of retained biological samples donated, the samples will be disposed of/destroyed, if not already analyzed.

The Principal Investigator will ensure that:

- Patient withdrawal of informed consent to the use of biological samples donated is notified immediately to Sponsor or Designee.
- Biological samples from the patient, if stored at the study site, are immediately identified, disposed of/destroyed and the action is documented.

The Sponsor has to ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent without delay and that the laboratory(ies) holding the samples ensures that samples are disposed of/destroyed or returned to the study site and the action is documented.

8.9 Pharmacodynamics

Not Applicable

8.10 Appropriateness of Measurements

All (other) methods used for safety assessments are commonly used in standard medical care.

9 Statistical Considerations

9.1 General Consideration

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed description of all statistical summaries, presentations and analyses will be outlined in the Statistical Analysis Plan (SAP), which will be finalized and approved prior to locking the database and unblinding.

The primary study objective is to estimate the X842 dose for Phase 3 study with good precision, and hence comparison of different doses of X842 to the active comparator arm (lansoprazole 30 mg) will not involve any formal statistical testing.

The primary analysis evaluating the dose-response relationship based on different doses of X842, as well as secondary analyses, will be based on the overall study population. In addition, the two subgroups, erosive esophagitis due to GERD LA grade C or D and erosive esophagitis due to GERD LA grade A or B who are partial responders to PPI treatment, will be evaluated separately.

All data measured on a continuous scale will be presented using summary statistics. Summary statistics is defined as number (N), arithmetic mean, standard deviation (SD), median, minimum Q1, Q3 and maximum value. Where appropriate 95% confidence intervals will be presented.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual patient data will be listed by patient number, treatment, and, where applicable, by assessment time.

9.2 Sample Size Determination

CCI

CCI

[redacted]

9.3 Populations for Analyses

For purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All patients who signed the ICF (including screening failures).
Full Analysis Set (FAS)	The full analysis set (FAS) will consist of all patients who have been randomized and received at least 1 dose of IMP. Patients will be analyzed according to randomized treatment (any randomized but not treated patient will be marked and reported as such).
Per Protocol Set (PPS)	The per protocol analysis set (PPS) will consist of all patients who have been randomized and completed the study without any major protocol deviations that are judged to compromise the analysis of the data. All protocol violations will be judged as major or minor, taking composite effects of protocol deviations into consideration, excluding patients for whom the clinical outcome is qualitatively affected by the protocol deviations.
Safety Analysis Set	The safety analysis set will consist of all patients who have been randomized and received at least 1 dose of IMP. Patients will be analyzed according to the treatment actually received (in case this differs from randomized treatment).

PK Analysis Set	The PK analysis set will consist of all patients who received at least 1 dose of IMP and have at least 1 measurement of plasma concentration of X842/linaprazan. Patients will be analyzed according to the treatment actually received (in case this differs from randomized treatment).

The FAS will be the primary analysis set for all efficacy analyses and the PPS will be used to demonstrate robustness of results for the primary efficacy endpoint(s).

9.4 Statistical Analyses

9.4.1 Patient Disposition

Patient disposition will be presented together with withdrawals from treatments, withdrawals from the study and the primary reason for withdrawal.

9.4.2 Protocol Deviations

Protocol deviations will be collected and reviewed during the study. The final classification and effect of each protocol deviation as well as the composite effect of a set of protocol deviations on analysis populations will be assessed prior to the database lock.

9.4.3 Demographics and Baseline Characteristics

Descriptive statistics for demographics, weight and height will be presented by treatment.

9.4.4 Medical/surgical History and Prior/Concomitant Medication

Medical/surgical history and prior/concomitant medications will be presented by treatment using descriptive statistics and listings.

9.4.5 Treatment Compliance

The number of patients treated, and their individual dose will be tabulated.

9.4.6 Physical Examination

Abnormal findings will be specified and presented by patient and summarized by treatment and period.

9.4.7 Efficacy Analyses

Analyses of the primary efficacy endpoint will be performed for both the FAS and PPS; analyses of the secondary and exploratory efficacy endpoints will be performed for the FAS only.

Endpoint	Statistical Analysis Methods
Primary	Analysis of primary endpoints will focus on the rate of esophageal mucosa healing in the four X842 dose groups to identify the dose that will lead to having 85% of the patients have esophageal mucosa healing after 4 weeks of treatment. It will involve dose-response modeling, evaluating a sequence of dose-response models for the healing rate including the Linear, Exponential, E_{max}, Sigmoid E_{max} and Logistic models (on logit scale). The models will be compared in terms of model fit, and the target dose estimated as the dose providing the target effect of 85% healing rate from the best fitting model will be derived. The data will be summarized and analyzed descriptively by treatment utilizing statistical summary tables and plots.
Secondary	The data will be summarized and analyzed descriptively by treatment utilizing statistical summary tables and plots for the below secondary efficacy endpoints: 1. Percentage of heartburn-free 24-hour days during the Weeks 1-8 (Visits 2-9) based on eDiary (RESQ-eDiary), including splits into day- and nighttime evaluations. 2. Percentage of 24-hour days with at most mild heartburn symptoms during the Weeks 1-8 (Visits 2-9) based on eDiary (RESQ-eDiary), including splits into day- and nighttime evaluations. 3. Investigator assessment of symptom at Weeks 1-8 (Visits 2-9) 4. Reflux related symptoms as measured by change from baseline in QOLRAD score assessed after 1, 2, 4 and 8 weeks of treatment
Exploratory	• Pre-dose plasma concentrations collected twice daily after 1, 2, and 4 weeks of treatment. The data will be summarized and analyzed descriptively by dose level utilizing statistical summary tables and plots. The evaluation will be based on the PK analysis set. • Association between esophageal mucosal healing and reflux related symptom pattern Reflux related symptom pattern as measured by change from baseline in daily diary completion by patients (RESQ-eDiary), investigator's assessment and QOLRAD after 1, 2 and 4 weeks of treatment will be summarized by status of observed healing at 4 weeks by treatment group. The data will be summarized and analyzed descriptively by treatment utilizing statistical summary tables and plots. The evaluation will be based on the FAS.

9.4.8 Safety Analyses

All safety analyses will be performed on the Safety Set.

Endpoint	Statistical Analysis Methods
Evaluate the safety and tolerability of the four dose levels of X842 and lansoprazole, where lansoprazole will serve as the active comparator.	Physical examination, weight, BMI, vital signs, electrocardiogram (ECG) recordings, safety laboratory measurements (hematology/clinical chemistry/urinalysis), adverse event (AE), treatment emergent adverse event (TEAE), adverse event of special interest (AESI), serious adverse event (SAE) reporting, concomitant medication(s).
Weight and BMI	Weight and BMI will be presented by patient and summarized by treatment using descriptive statistics along with absolute and percent change.
Vital signs	For BP and heart rate, descriptive statistics of actual values and change from screening will be used for summaries by treatment group and assessment day. Categorically classified (Normal/Abnormal) results will also be summarized.
12-lead ECG	ECG variables will be summarized according to actual values and change from screening using summary statistics and will be presented by treatment group and assessment visit. Categorically classified (Normal/Abnormal) results will also be summarized.
Safety laboratory analyses	All hematology, clinical chemistry and coagulation laboratory tests will be summarized using descriptive statistics for actual values and change from screening and presented by treatment group and assessment day for each study site separately (due to assays performed locally). Additionally, the local laboratory normal ranges will be used to classify the results as: High, Normal or Low and categorical summaries will be presented overall according to treatment group and assessment visit. Pooling across all sites is possible due to the categorical classification.
Adverse events	All AEs will be summarized according to TEAE or baseline symptom following classification of the verbatim terms according to the MedDRA dictionary. The number and percentage of patients for all classified events will be presented according to System organ class (SOC) and Preferred term (PT) by treatment group and overall. Separate summaries will be presented for all AEs by event frequency of occurrence and also for all AEs according to seriousness, severity and relationship. Separate summaries will be presented for AEs of Special Interest

9.4.9 Other Analyses

Descriptive statistics for the C-trough will be presented by treatment group with number of measurements, arithmetic mean, SD, CV, median, minimum, maximum, geometric mean, geometric CV%.

9.5 Interim Analyses

No interim analyses are planned for this study.

9.6 Data Monitoring Committee (DMC)

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Ethical Conduct of the Study

The study will be performed in accordance with the protocol and ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/good clinical practice (GCP) E6 (R2), EU Clinical Trials Directive, and applicable local regulatory requirements.

10.1.2 Ethics and Regulatory Review

The Coordinating Investigator in each country is responsible for submission of the CSP, the patient information and ICF, any other written information to be provided to the patients and any advertisements used for recruitment of patients to applicable IEC for approval.

The Sponsor or Designee is responsible for submission of study documents to the applicable CAs according to local regulatory requirements.

Approval must be obtained in writing from both IEC and CA before the first patient can be recruited.

The Sponsor will provide the CA, IEC and Principal Investigators with safety updates/reports according to local requirements. Progress reports and notifications of SUSARs will be provided to the IEC according to local regulations and guidelines.

10.1.3 Patient Information and Consent

It is the responsibility of the Investigator or an authorized associate to give each potential study patient (or the patient's legally acceptable representative and/or witness, as applicable) adequate verbal and written information before any study-specific assessments are performed.

The information will include the objectives and the procedures of the study as well as any risks or inconvenience involved. It will be emphasized that participation in the study is voluntary and that the patient may withdraw from participation at any time and for any reason, without any prejudice. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.

Before performing any study related procedures, the ICF must be signed and personally dated by the patient (or their legally acceptable representative and/or witness, as applicable) and by the Investigator. A copy of the patient information including the signed ICF will be provided to the patient.

By signing the ICF the patient should authorize the Investigator to use the endoscopy video/digital image taken prior to the ICF signature, to be the basis of eligibility evaluation and enrollment into the study.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the CRF. The patient information sheet and the signed ICF should be filed by the Investigator for possible future audits and/¬or inspections.

The final approved version of the patient information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

10.1.4 Patient Identification Card

The patient will be provided with a Patient Identification Card including the following information:

- That he/she is participating in a clinical study
- Patient study ID
- That he/she is treated with the IMP
- The name and phone number of the Investigator
- Name and address of the Sponsor

10.1.5 Patient Data Protection

The ICF includes information that data will be recorded, collected and processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC) and General Data Protection Regulation (GDPR), the data will not identify any persons taking part in the study.

The potential study patient (or the patient's legally acceptable representative and/or witness, as applicable) should be informed that by signing the ICF he/she approves that authorized representatives from Sponsor and Parexel, the concerned IEC and CA have direct access to his/her medical records for verification of clinical study procedures. This agreement is to be substantiated in a separate document, according to local requirements.

The patient has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete in accordance with the European Union Data Protection Directive (95/46/EC) and the request will be raised to the Principal Investigator.

The Investigator must file a Patient Identification List which includes sufficient information to link records, i.e. the CRF and clinical records. This list should be preserved for possible future inspections/audits but must not be made available to the Sponsor except for monitoring or auditing purposes.

Personal data that are collected in the study such as health information and ethnicity are considered as sensitive personal data. This data will be pseudoanonymized, i.e. personally identifiable information will be removed and replaced by a unique patient ID and will be processed by the Sponsor and other involved parties during the study. After the study end, only anonymized data, i.e. aggregated data sets, can be used.

For this study, the Sponsor is the data controller of all data processed during the study (e.g., trial master file [TMF], study reports) and Parexel is the data processor. Any subcontractors used in the study, are also data processors.

For data that are processed at the study sites (e.g., medical records and ISF), the respective study site is the data controller.

10.1.6 Audits and Inspections

Authorized representatives of Sponsor, a CA, or an IEC may perform audits or inspections at the study site, including source data verification (SDV). The purpose of an audit or inspection is to

systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP guidelines and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a CA about an inspection at the study site.

10.1.7 Data Quality Assurance

10.1.7.1 Quality management

10.1.7.1.1 Critical process, system and data identification

During protocol development, the Sponsor will identify those processes, systems (facilities, computerized systems) and data that are critical to ensure human patient protection and the reliability of trial results according to applicable SOPs and International Conference on Harmonization (ICH) E6 R2.

10.1.7.2 Quality assurance and quality control

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs with regards to management of identified risks, CSP compliance, GCP compliance and applicable regulatory requirements.

The Sponsor is responsible for securing agreements with involved subcontractors and to perform regular subcontractor oversight to ensure CSP compliance, GCP compliance and compliance with applicable regulatory requirements.

The Sponsor is responsible for implementing a risk-based validated electronic data capture system and maintain SOPs for the whole life- cycle of the system.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

10.1.8 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6 GCP, Section 8) for 10 years after finalization of the clinical study report (CSR). This includes any original source documents related to the study, the Patient Identification List (providing the sole link between named patient source records and anonymous CRF data), the original signed ICFs and detailed records of disposition of IMP.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The Sponsor will archive the Trial Master File in accordance with ICH E6 GCP, Section 8 and applicable regulatory requirements.

The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the clinic/investigational site and filed in the ISF for archiving for 10 years after finalization of the CSR. The completed original eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the Sponsor.

10.1.9 Study and Site Closure

The Sponsor or Designee reserves the right to discontinue the study at any time but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must inform all participating patients and perform relevant assessments, preferably according to the scheme for the final assessments. All delivered and unused study products and other study materials must be returned and all CRFs completed as far as possible.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

The study may be placed on hold for evaluation of possible risk to patients, prior to decision as to whether to terminate the study if any of the following criteria are met:

- At least 3 patients experience a similar unexpected AE, which is assessed as severe and is probable/possible related to the IMP.
- The occurrence of an SAE, if considered probable/possible related to the IMP.

A study termination will be initiated pending the outcome of any SAE investigation; termination will be based on the circumstances surrounding the event and findings with unblinding of the Sponsor medical monitor, if necessary.

The study will be discontinued for any of the following reasons:

- If overall 5 (five) X842-treated patients develop the same type of AESI and the frequency is at least 2 × higher than in the comparator group.
- If 3 (three) X842-treated patients meet Hy's Law criteria (≥ 3 × ULN for ALT or AST with total bilirubin ≥ 2 × ULN and no other explanation for these elevations).
- If one or more clinically significant, life-threatening, or significantly disabling/incapacitating events that are likely related to X842 and that, in the opinion of

the Investigator in consultation with the Sponsor, may constitute sufficient reason to stop the study.
- If the Sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.10 Publication Policy

The results from this study may be submitted for publication at the discretion of the Sponsor.

10.1.11 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/ CAs in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

Any proposed change to the approved Final CSP (including appendices) will be documented in a written and numbered clinical protocol amendment. All substantial amendments to the protocol must be approved by the appropriate IEC and/or CA before implementation according to applicable regulations.

10.1.12 Insurance

Patients will be covered under Cinclus Pharma AG clinical trial insurance policy. The copy of certificate of insurance and an information leaflet containing essential information about the insurance coverage will be provided to the study sites and can be provided to the patients upon request. The participating patients are also protected in accordance with national regulations, as applicable.

10.1.12.1 Access to source data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be

verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures Parexel and the Sponsor of the necessary support at all times.

10.2 Appendix 2: Study Management

10.2.1 Training of Study Site Personnel

Before enrolment of the first study patient a Sponsor representative or Designee will perform a study initiation visit at the study site. The requirements of the CSP and related documents will be reviewed and discussed, and the investigational staff will be trained in any study-specific procedures and system(s) utilized.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. A *Curriculum Vitae* will be available for all staff delegated study-specific duties.

10.2.2 Clinical Monitoring

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.

As defined in the risk-based monitoring plan, approved by the Sponsor and provided separately, the responsible CRA will periodically visit the study sites at times agreed upon by the Investigator and the CRA. At the time of each monitoring visit, the role of the CRA is (but not limited to) to:

- provide information and support to the investigational team.
- confirm that facilities and resources remain acceptable.
- confirm that the investigational team is adhering to the CSP, applicable SOPs, guidelines, manuals and regulatory requirements.
- verify that data are being accurately and timely recorded in the CRFs and that IMP accountability checks are being performed.
- verify that data in the eCRF are consistent with the clinical records (SDV) in accordance with the Monitoring Plan.
- verify that the correct informed consent procedure has been adhered to for participating patients.
- ensure that withdrawal of informed consent to the use of the patient's biological samples will be reported and biological samples are identified and disposed of/destructed accordingly, and that this action is documented and reported to the patient.
- verify that AEs are recorded and reported in a timely manner and according to the CSP.
- raise and escalate any serious quality issues, serious GCP breach and any data privacy breach to the Sponsor.

Remote monitoring will also be performed continuously by study team members at Parexel in accordance with the risk-based monitoring plan.

When the study has been completed and all queries have been resolved and the database has been locked, the CRA will perform a close-out visit.

10.2.3 Medical Monitoring

The role of medical monitoring in the clinical trial is to capture safety information in a complete and timely fashion and to recognize trends that may be indicative of hazards associated with study treatments. In addition, medical monitoring involves advising the project team and the investigators of medical and scientific issues related to the conduct of the trial.

The responsibilities of the Medical Monitor will be specified in the Medical Monitoring Plan and Safety Management Plan.

Potential drug-induced liver injury events require notification of the Medical Monitor (see Section 8.4.1.3).

10.2.4 Source Data Documents

A separate SDV List will be generated for each site before start of enrolment, specifying the location of the source of derived information appearing in the eCRF. This document must be signed by the Principal Investigator and the CRA to confirm agreement before start of recruitment.

Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verifies the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the trial. They include laboratory notes, memoranda, material dispensing records, patient files, etc. The eCRF is essentially considered a data entry form and should not constitute source data unless clearly specified in the SDV List.

The Investigator should guarantee access to source documents to the CRA, CAs and the IECs, if required.

10.2.5 Study Agreements

The Principal Investigator must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study.

Agreements between Sponsor and the study site must be in place before any study related procedures can take place, or patients be enrolled.

10.2.6 Study Timetable and End of Study

The study is expected to start in Quarter 3, 2020 (Final Study Protocol) and to be completed in Quarter 1, 2022 (Clinical Study Report).

All patients who participate in this study and complete Visit 9 (End of Study/Early Termination) visit are considered to have completed the study. The end of the study is defined as the date of the last visit of the last patient in the study.

10.2.7 Reporting and Publication

10.2.7.1 Clinical study report

A summarizing report must be submitted to the applicable CA and IEC within 12 months after completion of the study (in accordance with LVFS 2011:19, Chapter 9).

A CSR, in compliance with ICH E3 (Structure and content of clinical study reports) describing the conduct of the study, the statistical analysis performed, and the results obtained, will be prepared by Parexel. The report will be reviewed and approved by, as a minimum, the Principal Investigator, the Statistician and the Sponsor. The study results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the study.

10.2.7.2 Annual safety report

If the study duration exceeds 1 year, the Sponsor must submit an annual safety report to the CA and to the IEC. The report shall summarize all SAEs and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical study.

10.2.8 Confidentiality and Ownership of Study Data

Any confidential information relating to the IMP or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study are responsible for protecting the confidentiality of this proprietary information belonging to the Sponsor.

10.3 Appendix 3: Data Management

The data management routines include procedures for handling of eCRF, database set-up and management, data verification, quality control (QC) of the database, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the CSP and the eCRF specification.

Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of computerized online edit checks identifying e.g., data values that are outside the allowed range and SAS-programmed offline checks on data exports. All study-specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

Detailed information on data management will be described in a study-specific Data Management Plan (DMP).

10.3.1 The Web Based eCRF

All clinical data will be entered into a 21 CFR Part 11-compliant eCRF. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents or bedside (if the eCRF data constitutes source data). Source data are to be defined at the site before inclusion of the first patient.

Authorized site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all

authorized site personnel prior to the study being initiated and any data being entered into the system for any study patient.

The Investigator must submit a completed eCRF for each patient for whom Informed Consent has been obtained. Any supportive documentation submitted with the eCRF should be clearly identified with the Study ID and Patient Number. Any personal information, including name, should be removed or rendered illegible to preserve individual confidentiality.

10.3.2 The Entering of Data into the eCRF

All data should be entered in English. The eCRFs should be completed as soon as possible during or after the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that preferably same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or assigned study personnel should record such information in the eCRF. The Investigator will be required to electronically sign-off the clinical data. This will be performed by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature.

10.3.3 Electronic Patient Reported Outcome

The patients themselves will record data using an electronic patient reported outcome (ePRO) system (QOLRAD) linked to the eCRF and the clinical database. The ePRO system includes password protection and internal quality checks. Text reminders can be sent to the patient through the ePRO. All data registered in the ePRO are stored together with the eCRF data.

10.3.4 The Data Cleaning Process

The CRA will review the eCRFs and evaluate them for completeness and consistency. Each eCRF will be compared with the respective source documents to ensure that there are no discrepancies for critical data as described in the risk-based monitoring plan. All entries, corrections, and alterations are to be made by the Investigator or Designee. Neither the CRA nor any other study team member besides site staff can enter data in the eCRFs. Once clinical data have been saved, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged.

If additional corrections are needed, the responsible CRA or Data Manager or Medical Monitor will raise a data clarification in the eCRF. An appropriate member of the site personnel will

answer the data clarifications in the eCRF. This will be audit trailed electronically within the eCRF, meaning that the name of study personnel, time, and date is logged.

10.3.5 Audit Trail

All changes will be fully recorded in a protected audit trail. A reason for the change will be required.

10.3.6 External Data

External data consists of data that are not recorded in the eCRF. Data may be received in electronic format or as a paper printout. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed with the external data provider.

10.3.7 Medical Coding

Medical coding will be performed by trained personnel at Parexel. Adverse events and medical/surgical history verbatim terms are coded using the Medical Dictionary of Regulatory Activities (MedDRA; latest version available at start of coding). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Anatomic Therapeutic Chemical (ATC) classification system. All coding will be approved by Sponsor prior to database lock.

10.3.8 Database Lock

When all data have been entered and discrepancies solved, clean file will be declared, the database will be locked, and the data will be analyzed.

10.4 Appendix 4: Abbreviations and Trademarks

Abbreviation or term	Explanation
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALAT	Alanine aminotransferase
ALP	Alkaline phosphatase
ASAT	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration-time curve

AUC_{inf}	Area under the plasma concentration-time curve from 0 to infinity
AUC_{last}	Area under the plasma concentration-time curve from 0 to the last measured concentration
BID	Twice daily (bis in die)
BP	Blood pressure
BMI	Body mass index
CA	Competent authority
C_{max}	Maximum (peak) concentration
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Associate
CRF/eCRF	Case report form/electronic CRF
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CYP	Cytochrome P450
ECG	Electrocardiogram
EEA	European Economic Area
eGERD	Erosive gastro-esophageal reflux disease
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GDPR	General Data Protection Regulation
GERD	Gastro-esophageal reflux disease
GI	Gastrointestinal
Hb	Hemoglobin
IB	Investigator's Brochure
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
H	Hour
ICF	Informed consent form
ICH	International conference on harmonization
IEC	Independent ethics committee

IND	Investigational new drug
INR	International normalized ratio
IMP	Investigational medicinal product
ISF	Investigator site file
LA grade	The grade of esophagitis according to the Los Angeles classification system
LFT	Liver function test
LLOQ	Lower limit of quantification
MAD	Multiple ascending dose
MedDRA	Medical dictionary for regulatory activities
Min	Minute
Ms	Millisecond
N	Number
NOAEL	No observed adverse effect level
o.m.	Every morning
OTC	Over-the-counter
P-CAB	Potassium-competitive acid blocker
PD	Pharmacodynamic
PDILI	Potential drug-induced liver injury
PK	Pharmacokinetic
pKa	acid dissociation constant
PPI	Proton-pump inhibitor
PPS	Per protocol analysis set
PRO/ePRO	Patient reported outcome/electronic PRO
PT	Preferred term
QD	Once daily (quaque die)
QOLRAD	Quality of Life in Reflux and Dyspepsia
RBC	Red blood cell
RESQ-eD	Reflux Symptom Questionnaire electronic Diary
S	Second
SAD	Single ascending dose
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SD rats	Sprague-Dawley rats

SDV	Source data verification
SOC	System organ class
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
TIPS	Transjugular intrahepatic portosystemic shunt
T_{max}	Time after drug administration when the maximum plasma concentration is reached
$T_{½}$	Half-life
TMF	Trial master file
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

10.5 Appendix 5: Important Medical Procedures to be Followed by The Investigator

10.5.1 Medical Emergencies Contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such. Detailed SAE reporting procedures are included in Section 8.4.6.

In the case of a medical emergency the Investigator may contact the Medical Responsible Person at Cinclus Pharma AG or a representative from Parexel.

Name	Function in the study	Telephone number and e-mail
PPD	PPD	PPD

10.6 Appendix 6: Study Administrative Structure

Sponsor
Cinclus Pharma AG
Gartenstrasse 101
CH-4002 Basel, Switzerland

Sponsor's Medical Representative
PPD

PPD

PPD

PPD

Sponsor's Chief Scientific Officer
PPD PPD

E-mail

Study management
Parexel International

10.7 Appendix 7: Declaration of Helsinki

http://www.up.ac.za/media/shared/Legacy/sitefiles/file/45/2875/declarationofhelsinki_fortaleza_brazil2013.pdf

10.8 Appendix 8: Los Angeles Classification of Reflux Esophagitis

Grade A	One (or more) mucosal break(s) no longer than 5 mm, that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break(s) more than 5 mm long, that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break(s) that is continuous between the tops of two or more mucosal folds, but which involve(s) less than 75% of the oesophageal circumference
Grade D	One (or more) mucosal break(s) which involve(s) at least 75% of the oesophageal circumference

10.9 Appendix 9: Medications that may Interact with X842 or Linaprazan

CYP3A inhibitors	CYP3A4 inhibitors: grapefruit juice and other juices such as Seville oranges, cranberry juice Strong CYP3A4 inhibitors: ketoconazole, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, conivaptan, nefazodone, protease inhibitors, antivirals Moderate CYP3A inhibitors: erythromycin, fluconazole, darunavir, diltiazem, dronedarone, crizotinib, aprepitant, casopitant, imatinib, verapamil, netupitant, nilotinib, tofisopam, cyclosporine, ciprofloxacin, isavuconazole, cimetidine
CYP inducers	St John's Wort, rifampicin, carbamazepine, phenytoin, rifapentine, rifabutin, smoking
CYP1A2 inhibitors	ciprofloxacin, enoxacin, clinafloxacin, fluvoxamine
CYP2B6 inhibitors	voriconazole, ticlopidine, disulfiram, clopidogrel, rolapitant, prasugrel, hormone replacement therapy with estrogen or progesterone
CYP2C8 inhibitors	gemfibrozil, clopidogrel

CYP3A substrates	alfentanil, alisporivir, almorexant, alpha-dihydroergocryptine, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, blonanserin, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, cobimetinib, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eliglustat (in subjects CYP2D6 PMs), elvitegravir, eplerenone, everolimus, felodipine, grazoprevir, ibrutinib, indinavir, isavuconazole, ivabradine, ivacaftor, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, sirolimus, tacrolimus, terfenadine, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin, hormone based contraceptives*
CYP2C19 substrates	pantoprazole, hexobarbital, mephobarbital, omeprazole, lansoprazole, mephenytoin, diazepam, gliclazide, proguanil (prodrug), rabeprazole
CYP2C9 substrates	Warfarin
BCRP substrates	anthracyclines, daunorubicin, doxorubicin, topotecan, irinotecan, methotrexate, imatinib, mitoxantrone, nucleoside analogs, prazosin, pantoprazole, topotecan, rosuvastatin, teriflunomide, chlorothiazide
P-gp Substrates	dabigatran etexilate, digoxin, fexofenadine, sofosbuvir
OATP1B1 substrates	repaglinide, pravastatin, rosuvastatin, fluvastatin, pitavastatin, lovastatin, simvastatin, bosentan, irinotecan, olmesartan, enalapril, temocaprilat, valsartan, docetaxel

Abbreviations
CYP: cytochrome P450; BCRP: breast cancer resistance protein; P-gp: P-glycoprotein; OATP1B1: organic anion transporting polypeptide 1B1
* Except for patients using hormonal contraception defined in Exclusion criterion #1

10.10 Appendix 10: COVID-19 Specifics

There is currently an outbreak of the disease COVID-19 caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

EMA and FDA have issued guidelines to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is

evolving, guidelines, recommendations, national regulations and local restrictions may change. Given the circumstances of potentially relapsing pandemic or epidemic situation regarding the spread of COVID-19 in future, special attention will be paid to protect patients enrolling in the study and site staff involved in the investigations against infection.

Risk mitigation measures:

- Current country level regulations and local recommendations for prevention of pandemic will be strictly adhered to.
- Patient enrollment in the study will commence only when the Sponsor and CRO in collaboration deem it is safe to start the study.
- Patients participating in the study will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat and fatigue throughout the study. Body temperature measurement and respiratory rate will be captured during vital signs examinations as designated on the Schedule of Assessments.
- Patients participating in the study and site personnel will be advised to adhere to local requirements for reduction of the public viral exposure.
- Confirmation of COVID-19 infection should follow current local regulations and guidance.

The guidance from the Regulatory Authorities may continue to evolve throughout the pandemic and Investigators are encouraged to check for updates regularly. Also, as the situation evolves COVID-19 related clinical trial measures may be continuously adjusted in line with local regulations, guidance and needs.

References

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Investigator Agreement Page

Declaration of the Principal or Global Coordinating Investigator

This page should be used for studies with EU sites, but is not mandatory for US studies.

Title: A randomized double-blind, double dummy, active comparator-controlled dose-finding study in patients with erosive esophagitis due to gastro-esophageal reflux disease (GERD) Los Angeles grade C or D, and patients with at least partial symptom response but endoscopically still unhealed after 8 weeks history of standard treatment healing course with proton-pump inhibitor (PPI), to investigate safety, tolerability, and healing rates after 4 weeks treatment of X842 or lansoprazole, and symptom pattern during subsequent 4 weeks treatment with lansoprazole

Note that Investigator sign-off is required for compliance with GCP, but it is the Sponsor's (or Designee's) responsibility to get this. It is not the responsibility of MWS but the Parexel team may obtain Investigator sign-off if requested by the Sponsor. Use "Principal Investigator" only when there is just one center.

Principal or Global Coordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Declaration of the Investigator

Title: A randomized double-blind, double dummy, active comparator-controlled dose-finding study in patients with erosive esophagitis due to gastro-esophageal reflux disease (GERD) Los Angeles grade C or D, and patients with at least partial symptom response but endoscopically still unhealed after 8 weeks history of standard treatment healing course with proton-pump inhibitor (PPI), to investigate safety, tolerability, and healing rates after 4 weeks treatment of X842 or lansoprazole, and symptom pattern during subsequent 4 weeks treatment with lansoprazole

Responsible Investigator of the Local Study Center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

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Institution (block letters)

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Phone number