CLINICAL STUDY PROTOCOL

Cover Page

Protocol No.:	ITOP-322-0216	**Protocol Date:**	05-SEP-2023
Study Title:	A randomized, multicentre, parallel–group, open-label, active-controlled study to investigate the non-inferiority of Itopride Hydrochloride 150mg extended release tablets once daily versus Itopride Hydrochloride 50 mg film coated tablets thrice daily in subjects with gastrointestinal symptoms caused by gastric dysmotility and delayed gastric emptying like bloating sensation, early satiety, postprandial fullness, upper abdominal pain or discomfort, anorexia, heartburn, nausea, and vomiting in functional (non-ulcer) dyspepsia or chronic gastritis.		
IND No.:	Not applicable		
EudraCT No.:	Not applicable		
Phase of Development:	III		
Sponsor:	Abbott Healthcare Products B.V., Weesp, The Netherlands		
Global Clinical Director:	Suntje Sander-Struckmeier		
Protocol Author(s) Name & Contact Details:	Suntje Sander-Struckmeier, Elke Kahler Abbott Laboratories GmBH, Hannover, Germany		

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Protocol Signature Page

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Sponsor: Abbott Healthcare Products B.V.

Global Clinical Director: Suntje Sander-Struckmeier

Protocol Author(s) Name & Contact Details: Suntje Sander-Struckmeier, Elke Kahler
Abbott Laboratories GmbH, Hannover, Germany

Sponsor Representative:

Suntje Sander-Struckmeier Date
Global Clinical Director
Abbott Laboratories GmbHFreundallee 9A
30173 Hannover
Germany

BY SIGNING BELOW, I, THE INVESTIGATOR, AGREE TO CONDUCT THE CLINICAL RESEARCH STUDY AS DESCRIBED IN THIS PROTOCOL.

Investigator:

<name> Date
<affiliation/institution>
<city, state/province, country>

SYNOPSIS

Name of Sponsor: Abbott	**Name of Finished Product:** Itopride Hydrochloride 150mg extended release tablets	**Name of Active Ingredient(s):** Itopride

Title of Study:

A randomized, multicentre, parallel–group, open-label, active-controlled study to investigate the non-inferiority of Itopride Hydrochloride 150 mg extended release once daily versus Itopride Hydrochloride 50 mg film coated tablets thrice daily in subjects with gastrointestinal symptoms caused by gastric dysmotility and delayed gastric emptying like bloating sensation, early satiety, postprandial fullness, upper abdominal pain or discomfort, anorexia, heartburn, nausea, and vomiting in functional (non-ulcer) dyspepsia or chronic gastritis.

Study Duration: Approximately 21 months. The enrolment period is estimated to be approximately 8 months from first subject screened.	Phase of Development: III

Objectives:

Primary objective(s):

To assess the comparable efficacy of Itopride Hydrochloride 150 mg extended release tablet (administered once daily) and Itopride Hydrochloride 50 mg film coated tablets (administered TID) after 8 weeks treatment.

Secondary objective(s):

- To assess the comparable efficacy of Itopride Hydrochloride 150 mg extended release tablet (administered once daily) and Itopride Hydrochloride 50 mg film coated tablets (administered TID) after 4 weeks treatment.
- To assess quality of life for the two treatment arms using Disease Specific Quality of Life (Short Form - Nepean Dyspepsia Index SF-NDI) at baseline and end of treatment
- To assess the symptomatology (sensation of bloating, early satiety, postprandial fullness, upper abdominal pain or discomfort (epigastric pain, epigastric burning), anorexia (loss of appetite), heartburn, nausea and vomiting) of the disease in both treatment arms after 4 and 8 weeks of treatment.

Name of Sponsor: Abbott	**Name of Finished Product:** Itopride Hydrochloride 150mg extended release tablets	**Name of Active Ingredient(s):** Itopride

- To assess the number of responders of adequate/satisfactory relief from FD symptoms.

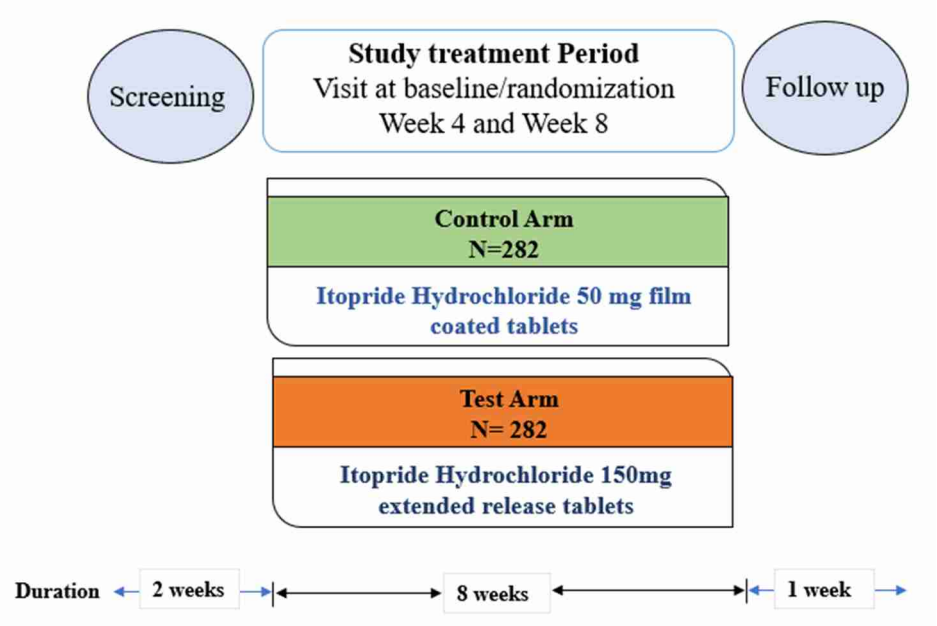
Exploratory objective(s):

- Treatment acceptance by subjects using 5-point Likert scale at the end of the treatment

Safety objective(s):

- To evaluate safety and tolerability in both treatment arms

Methodology:



Number of Subjects (Planned):

Number of subjects to be allocated to treatment: 564 (N= 282 per arm).

Number of subjects to be screened: Approx.700

Name of Sponsor: Abbott	**Name of Finished Product:** Itopride Hydrochloride 150mg extended release tablets	**Name of Active Ingredient(s):** Itopride

Diagnosis and Main Criteria for Inclusion:

1. Adult male and/or non-pregnant non-lactating female subjects aged above 18 years.
2. Subjects provided written informed consent and are willing to participate in the study.
3. Subjects with functional (non-ulcer) dyspepsia according to Rome IV criteria including postprandial distress syndrome (PDS) and with or without EPS (epigastric pain syndrome) with one or more of the following:
   -bothersome postprandial fullness,
   -bothersome early satiation
   -bothersome epigastric pain,
   -bothersome epigastric burning
   for at least 12 weeks in the preceding 6 months
4. No evidence of organic, systemic, metabolic or structural disease likely to explain symptoms - Subjects who have to undergone physical examination and lab tests (including white-cell and red-cell counts, measurement of fasting blood sugar and liver-function tests), abdominal ultrasonography, and upper GI endoscopy* in order to rule out structural cause for symptoms of FD.
   *history of upper GI endoscopy within 6 months prior to enrolment or at screening.
5. Baseline severity of at least moderate symptoms on LDQ (total score ≥ 9) at screening.
6. H. pylori negative documented test report within 3 months prior to enrolment or during screening.

Main Criteria for Exclusion

1. Known hypersensitivity to Itopride or any component of the formulation and to any other related drug.
2. Subject with history or presence of clinically relevant evidence of cardiovascular, neurological, gastrointestinal/hepatic, renal, psychiatric, respiratory, urogenital, hematologic/immunologic, HEENT (head, ears, eyes, nose, throat), dermatological/ connective tissue, musculoskeletal, metabolic/nutritional, drug hypersensitivity, allergy, endocrine, major surgery or other relevant disease as revealed by medical history requiring treatment which at investigator's discretion might interfere with the study..
3. Subjects who cannot be treated with Itopride in line with the prescribing information

Name of Sponsor: Abbott	**Name of Finished Product:** Itopride Hydrochloride 150mg extended release tablets	**Name of Active Ingredient(s):** Itopride

4. Subjects scheduled for surgery during the study.
5. Subjects with a history of difficulty in swallowing.
6. Subject requiring concomitant treatment with anticholinergic drugs, drugs with narrow therapeutic index, sustained release or enteric-coated formulations.
7. Subjects taking Acid release inhibitors (e.g. histamine-2-receptor [H2]- antagonists, proton pump inhibitors [PPI], or potassium-competitive acid blockers), antacids (e.g. aluminium- or magnesium hydroxide, sodium bicarbonate), gastric mucosa protectors (e.g. sucralfate, rebamipide).
8. Subject with history of unusual bleeding and family history for bleeding disorders.
9. Subjects with only reflux-related symptoms or who have predominantly reflux-related symptoms.
10. Subjects with esophagitis, Barrett`s esophagus, erosions or peptic ulcer disease within one year prior to the study or Zollinger-Ellison Syndrome.
11. Dyspepsia that is exclusively relieved by defecation or associated with a change in stool frequency or stool form to exclude IBS.
12. Clinically significant ECG abnormalities.
13. Subjects treated with Itopride or any other gastroprokinetic within 4 weeks prior to screening.
14. Subjects who took non-steroidal anti-inflammatory drugs for more than 2 weeks prior to screening
15. Subjects with refractory FD[1] (defined as FD presenting symptoms continuing for at least 6 months, unresponsive to at least two medical treatments such as PPIs, prokinetics, or H. pylori eradication) as per investigator's discretion
16. History of or known inflammatory bowel disease (IBD) or coeliac disease.
17. History of or known severe hepatic, renal, pancreatic, cardiac, metabolic, hematological or malignant disease or trimethylaminuria.
18. Subjects with changed smoking status within the last three months.
19. History of or known GI malignancy or ulcers associated to malignancy or any alarm features for GI malignancy, e.g. GI bleeding.
20. Subjects who do not meet the criteria stated in concomitant medication section.
21. Subjects with history of severe depression, anxiety or other psychological disorders.
22. Females with child-bearing potential must agree to use an acceptable method of contraception during the study.

Name of Sponsor: Abbott	**Name of Finished Product:** Itopride Hydrochloride 150mg extended release tablets	**Name of Active Ingredient(s):** Itopride

23. Subjects in whom an increase in gastrointestinal motility could be harmful, e.g., (history of) gastrointestinal hemorrhage, mechanical obstruction or perforation.
24. Specific food intolerance which is relieved by diet modifications (e.g. lactose intolerance, celiac disease).
25. Subjects with confirmed IBS as per Rome IV criteria.
26. Current alcohol or drug abuse.
27. History of abdominal surgery except appendectomy, cholecystectomy or hysterectomy, tubal ligations, bladder slings or vasectomies.
28. Hepatic cirrhosis or abnormal liver laboratory findings (defined as >3xULN of ALT or AST).
29. Subjects under hemodialysis therapy or having advanced chronic kidney disease (defined as eGFR <60 mL/min).
30. History of or known congestive heart failure NYHA class III and IV, or any other uncontrolled chronic diseases, such as: uncontrolled hypertension (systolic/diastolic blood pressure ≥160/100 mmHg); uncontrolled diabetes (HbA1c >8%).
31. Subjects currently being known to be afflicted by serious infection(s), or any known severe illness(es) which are judged by the investigator could interfere with subjects' safety and/or study evaluation.

Duration of Treatment:

8 weeks

Reference Therapy, Dose and Mode of Administration:

Test group - Itopride Hydrochloride 150 mg extended release tablets once daily before one of the main meals (preferably the same meal throughout the treatment)

Active Control group - Itopride Hydrochloride 50 mg film coated tablets 3 times daily before meals

Ganaton/Ganaton OD/Elthon/Elthon OD is the Abbott brand name for Itopride Hydrochloride in most countries and it may vary in some countries.

Criteria for Evaluation:

Efficacy:

Primary endpoint(s):

Name of Sponsor: Abbott	**Name of Finished Product:** Itopride Hydrochloride 150mg extended release tablets	**Name of Active Ingredient(s):** Itopride

Change in the overall severity of functional dyspepsia between baseline and week 8, as measured by the Leeds Dyspepsia Questionnaire (LDQ) severity score

Secondary endpoint(s):

- Change in the overall severity of functional dyspepsia between baseline and week 4, as measured by the Leeds Dyspepsia Questionnaire (LDQ) severity score
- Disease Specific Quality of Life (Nepean Dyspepsia Index NDI) assessed at baseline and week 8
- Change from baseline of NRS 11 score for symptoms (sensation of bloating, early satiety, postprandial fullness, upper abdominal pain or discomfort (epigastric pain, epigastric burning), anorexia (loss of appetite), heartburn, nausea and vomiting) after 4 and 8 weeks of treatment
- Responder analysis for adequate/satisfactory relief as assessed by LDQ and/or NRS 11
- Treatment acceptance and ease of use assessed by subjects using 5-point Likert scale

Safety:

- To evaluate the safety and tolerability of the two treatments by assessing the following safety endpoints: Treatment emergent adverse events (TEAEs) as detected by physical examination, laboratory assessments and vital signs.

Statistical Methods:

Efficacy

Primary efficacy:

- An ANCOVA analysis will be performed with the change in the LDQ score as dependent variable and treatment group, site and LDQ baseline value as additional factors. The difference between the two treatment groups will be calculated for the non-inferiority comparisons, together with a two-sided 95% confidence interval. Non-inferiority will be considered achieved if the lower bound of the 95% confidence interval of the difference between the two groups is greater than 1.75 (NI-margin). Normal approximation will be assumed for the parametric analyses. The primary analysis will be performed for both the per protocol set and the full analysis set. The analysis for the per-protocol set will be regarded as primary.

Name of Sponsor: Abbott	**Name of Finished Product:** Itopride Hydrochloride 150mg extended release tablets	**Name of Active Ingredient(s):** Itopride

Secondary efficacy:

- Full analysis sample will be used for the analysis of the secondary endpoints.
- All secondary efficacy variables will be assessed using descriptive statistics.
- In addition, the change from baseline in LDQ score at week 4 and the NRS 11 score for each symptom will be evaluated using the same analysis as specified for the primary endpoint.

Safety

- The safety sample will be used for the analysis of the safety and tolerability data. Adverse Events, laboratory values and vital signs will be analyzed descriptively.

Interim analysis

Not applicable

Sample size

Assumptions for sample size calculation are based on the studies of Holtmann et al.[2] and Talley et al.[3] from which a standard deviation of 7 can be assumed for the change of the LD questionnaire.

For the NI margin following assumptions were made:

- In the Holtmann study[2], a difference to placebo of 2 (95% CI: 0.03-3.97) in the LDQ was reported.
- In the Ang publication[4] (2011), a difference of 10-15% to placebo is regarded as clinically relevant
- NI-margin needs to be lower than 2. A difference of 15% results in 1.74. Therefore, a NI margin of 1.75 is chosen.

Assuming a NI margin of 1.75 and standard deviation of 7 for the change in the LDQ severity score, 253 subjects per treatment arm are required to conclude non-inferiority between the 2 treatment groups with a power of 80% at α-level of 2.5% single sided. Adding a 10% drop-out rate the total sample size would be 564 subjects (N= 282 per arm).

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of Covariance
ASEAN	Association of Southeast Asian Nations
AUC	Area under curve
ALT	Alanine amino transferase
AST	Aspartate amino transferase
ATC	Anatomical Therapeutic Chemical
BPP	Biostatistics project Planning and Programming
CDM	Clinical Data Management
CFR	Code of Federal Regulations
CRF	Case report form (paper or other media)
CRO	Contract research organization
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EPS	Epigastric pain syndrome
eCRF	electronic Case report form
FA	Full analysis
FGID	Functional Gastrointestinal Disorders
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practices
GERD	Gastroesophageal Reflux Disease
GPV	Global Pharmacovigilance
HLT	Highest level term
HLGT	High level group term
IB	Investigator's Brochure

IBD	Inflammatory bowel disease
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IR	Immediate release
IRB	Institutional Review Board
LDQ	Leeds Dyspepsia Questionnaire
LDH	Lactate dehydrogenase
LLT	Lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
NI	Non-inferior
NDI	Nepean Dyspepsia Index
NRS	Numerical Rating Scale
NYHA	New York Heart Association
OD	Once daily
PAGI-QoL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PP	Per-protocol
PPI	Proton pump inhibitor
PT	Preferred term
PDS	Postprandial distress syndrome
RSI	Reference safety information
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SBP	Systolic blood pressure
SF NDI	Short Form - Nepean Dyspepsia Index
SD	Standard Deviation
SSRI	Selective serotonin reuptake inhibitors
SNRI	Serotonin and norepinephrine reuptake inhibitors

SOC	System organ class
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse events
TID	Ter in die (Three times a day)
UD	Uninvestigated dyspepsia

1 ETHICS

1.1 Independent Ethics Committee or Institutional Review Board

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) is responsible for obtaining written approval for the clinical study protocol (including all substantial protocol amendments), the written subject informed consent form (including written assent, when applicable), informed consent updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects from an Independent Ethics Committee (IEC) / Institutional Review Board (IRB) that complies with the local regulatory requirements.

Written approval of the study must be obtained from the IEC/IRB prior to the study being implemented (i.e., shipment of clinical supplies to the Investigator or screening of subjects). Copies of the approval documentation will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the designated study documentation files.

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) will submit written reports of the clinical study status to the IEC/IRB annually, or more frequently if requested by the IEC/IRB. A final study notification should be forwarded to the IEC/IRB within 90 days after the study has completed, or in the event of premature termination of the study, within 15 days with the rationale for study termination clearly explained. Copies of all clinical study status reports (including termination) will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the study documentation files.

In accordance with national provisions or regulations, the Sponsor (or an authorized representative) will inform all participating IECs/IRBs and national authorities of all SAEs/SADRs/SUSARs or other safety-related information, which occur during the clinical study.

1.2 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations to assure that the rights, safety, and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

1.3 Subject Information and Consent

Voluntary written informed consent will be obtained from each subject prior to performing any study-related procedures. Each subject will be given both verbal and written information describing the nature and duration of the clinical study. The informed consent process will take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation in the study. Subjects will not be screened or treated until the

subject has signed an approved informed consent written in a language that is understandable to the subject.

The IEC/IRB approved informed consent form will be signed and personally dated by the subject (or legally acceptable representative, when appropriate) and the person who conducted the informed consent discussion. Each subject is to receive a copy of the signed and dated written informed consent form and any other written subject information.

The signature of an impartial witness is to be obtained in the event the subject or the subject's legally acceptable representative is unable to read. Additional signatures on the informed consent form may be required in accordance with IEC/IRB requirements or those of the Sponsor (or an authorized representative).

The Investigator is responsible for assuring the appropriate content of the informed consent form and that informed consent is obtained from each subject in accordance with the applicable regulations and guidelines. The original signed informed consent is to be retained in the study documentation files.

The Investigator shall maintain a log of all subjects who sign the informed consent form and indicate if the subject received study drug or, if not, the reason why. The subject's medical records should also document that the informed consent form was signed and dated prior to any study-related procedures being performed.

2 INTRODUCTION

Dyspepsia is defined as the episodic and persistent symptoms of the upper gastrointestinal tract. It is the medical term for difficult digestion. Dyspepsia is associated with various symptoms which include bloating, fullness, heartburn, early satiation, nausea, vomiting and abdominal pain[1].

The global prevalence of dyspepsia is at least 20%[5]. In the meta analysis done by Ford AC et al[5] overall pooled prevalence in all studies was 20.8% (95% CI 17.8% to 23.9%). The prevalence varied according to country (from 1.8% to 57.0%) and criteria used to define dyspepsia. The greatest prevalence values were found when a broad definition of dyspepsia (29.5%; 95% CI 25.3% to 33.8%) or upper abdominal or epigastric pain or discomfort (20.4%; 95% CI 16.3% to 24.8%) were used. The prevalence was higher in women (OR 1.24; 95% CI 1.13 to 1.36), smokers (OR 1.25; 95% CI 1.12 to 1.40), non-steroidal anti-inflammatory drug (NSAID) users (OR 1.59; 95% CI 1.27 to 1.99) and Helicobacter pylori-positive individuals (OR 1.18; 95% CI 1.04 to 1.33).

The worldwide prevalence of uninvestigated dyspepsia (UD) varies from 7% to 34%, with a pooled UD prevalence from 21 Southeast Asian studies of 21.6%. The variation in UD prevalence seems to be related to the different definitions of UD used in individual surveys. Approximately 25% of dyspepsia cases have an underlying organic cause. In Thailand, the prevalence of dyspepsia is 66%. Of those, 60–90% show no evidence of structural disease on endoscopy, i.e. functional dyspepsia (FD)[6]. A study from India reported prevalence of dyspepsia to be 30.4%[7].

The prevalence of dyspepsia varies considerably between different populations. Using the definition 'upper abdominal pain', the lowest UD prevalence of 7%-8% is seen in Singapore, South East Asia. Slightly higher rates are seen amongst the Scandinavians (14.5%) prevalence rates of 23-25.8% are seen in the US, with 30.4% population in India and New Zealand (34.2%) having the highest rates. Using the definition 'upper gastrointestinal symptoms', a lower prevalence was seen in Spain (23.9%), 32% UD prevalence rate was noted in the US whilst significantly higher rates of 38%-41% were noted in the UK and 45% in Nigeria[8].

Based on the causes, dyspepsia is classified into two main categories, namely organic and Functional Dyspepsia (FD). Organic dyspepsia includes peptic ulcer and Gastroesophageal Reflux Disease (GERD) as most identifiable cause. On the other hand, FD which is one of the most prevalent Functional Gastrointestinal Disorders (FGIDs) is identified by pathophysiological mechanisms such as delayed gastric emptying, impaired gastric accommodation to a meal, burning sensation in the epigastrium, hypersensitivity to gastric distension, predominant epigastric pain, early satiety and feeling of fullness during or post meals[4,9-10]

Globally, most dyspepsia patients fall into the category of FD, also known as the non-ulcer dyspepsia. FD is further subdivided into two diagnostic categories of meal-induced dyspeptic symptoms [Postprandial Distress Syndrome (PDS), characterized by postprandial fullness and early satiation] and Epigastric Pain Syndrome [(EPS), characterized by epigastric pain and burning][11-12].

Large population-based studies revealed that the prevalence of FD ranges from 10% to 30% worldwide[13]. FD prevalence decreases with age, from 9.5% in those aged 18–35 years to 3.9% in those aged over 65 years. Dyspeptic symptoms are more common in women, smokers, and those taking non-steroidal anti-inflammatory drugs[9].

Several pharmacological and non-pharmacological therapies with aim to reduce the symptoms and severity of functional dyspepsia and to improve the health-related quality of life in these patients are available, with some being more effective than others such as reassurance, diet, acid suppression, prokinetics, fundic relaxors, tricyclic antidepressants, rifaximin, and psychological therapy[14]. For patients younger than 60 years old, H. pylori test should be performed. For patients testing negative or not responding to H. pylori eradication, an initial trial of proton pump inhibitor (PPI) therapy is recommended; if ineffective, tricyclic antidepressants or prokinetic agents may be tried[9].

Itopride is indicated for the treatment of gastrointestinal symptoms caused by gastric dysmotility and delayed gastric emptying, such as the sensation of bloating, early satiety, postprandial fullness, upper abdominal pain or discomfort, anorexia, heartburn, nausea, and vomiting; functional (non-ulcer) dyspepsia or chronic gastritis. Eighteen randomized controlled trials (RCTs) (six placebo-controlled and 12 reference controlled), including a total of 4410 patients, and two meta-analyses, each including approximately 2500 patients, provide evidence of the efficacy of itopride in FD subjects.

The purpose of this study is to investigate the non-inferiority of Itopride Hydrochloride 150mg extended release tablets vs 3 times Itopride Hydrochloride 50 mg film coated tablets in subjects with gastrointestinal symptoms caused by gastric dysmotility and delayed gastric emptying, like bloating sensation, early satiety, postprandial fullness, upper abdominal pain or discomfort, anorexia, heartburn, nausea and vomiting in functional (non-ulcer) dyspepsia or chronic gastritis.

3 STUDY OBJECTIVES

3.1 Primary Objective(s)

To assess the comparable efficacy of Itopride Hydrochloride 150 mg extended release tablet (administered once daily) and Itopride Hydrochloride 50 mg film coated tablets (administered TID) after 8 weeks' treatment.

3.2 Secondary Objective(s)

- To assess the comparable efficacy of Itopride Hydrochloride 150 mg extended release tablet (administered once daily) and Itopride Hydrochloride 50 mg film coated tablets (administered TID) after 4 weeks treatment.
- To assess quality of life for the two treatment arms using Disease Specific Quality of Life (Nepean Dyspepsia Index NDI) at baseline and end of treatment
- To assess the symptomatology (sensation of bloating, early satiety, postprandial fullness, upper abdominal pain or discomfort (epigastric pain, epigastric burning), anorexia (loss of appetite), heartburn, nausea and vomiting) of the disease in both treatment arms after 4 and 8 weeks of treatment.
- To assess the number of responders of adequate/satisfactory relief from FD symptoms.

3.3 Exploratory Objective(s)

- Treatment acceptance by subjects using 5-point Likert scale at the end of treatment

3.4 Safety Objective(s)

- To evaluate safety and tolerability in both treatment arms

4 STUDY DESIGN

4.1 Overall Study Design and Plan-Description

This is a Phase 3, randomized, open-label, multicenter, parallel-group, active-controlled study to evaluate the non-inferiority efficacy of Itopride Hydrochloride 150mg extended release tablet (administered once daily) compared to Itopride Hydrochloride 50 mg film coated tablets

(administered TID) in subjects with gastrointestinal symptoms caused by gastric dysmotility and delayed gastric emptying, like sensation of bloating, early satiety, postprandial fullness, upper abdominal pain or discomfort, anorexia, heartburn, nausea and vomiting; functional (non-ulcer) dyspepsia or chronic gastritis.

This study will enroll 564 subjects (282 subjects in each arm) and the duration of subject participation will be approximately 11 weeks.

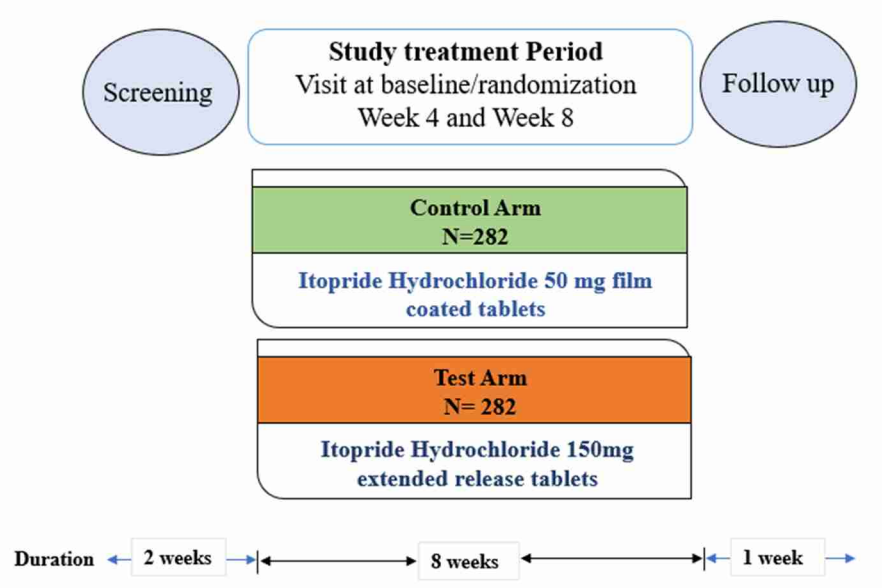
Screening will be carried out to evaluate the eligibility criteria. Upper GI endoscopy will be conducted to rule out any organic, structural disease. The upper GI endoscopy report should be within 6 months prior to randomization. If it is >6 months old, then it will be performed during screening.

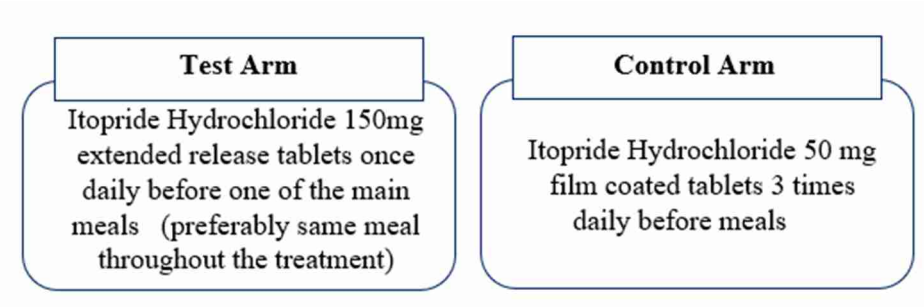
After screening, subjects will be randomized in a 1:1 ratio to one of the following treatment groups:

- Test group - Itopride Hydrochloride 150 mg extended release tablets once daily before one of the main meals (preferably the same meal throughout the treatment)
- Active Control group - Itopride Hydrochloride 50 mg film coated tablets 3 times daily before meals

The study drugs will be administered, as mentioned above, for a period of 8 weeks.

The investigator or designee will explain the study to potentially interested subjects in detail, and if they voluntarily agree to participate in the study, consent will be obtained. After meeting the eligibility criteria, subjects will be enrolled in the study and will be assigned Unique Identification Numbers (UINs) to maintain confidentiality.





The study drugs will be administered, as mentioned above, for a period of 8 weeks.

The endpoints will be evaluated at study visits as mentioned in section 8.

The investigator may repeat any test specified in the protocol, if needed, during the 14-day screening period.

A subject may be re-screened only after agreement with Sponsor representative and the subject may then have to undergo all screening procedures again as per protocol. In case of re-screening, the informed consent has to be collected again.

4.2 Discussion of Study Design, Including the Choice of Control Groups

This is an open label, randomized, multicenter, parallel-group, active-controlled Phase 3 study to evaluate the non-inferiority/ comparative efficacy of Itopride Hydrochloride 150 mg extended release tablets (administered once daily) compared to Itopride Hydrochloride 50 mg film coated tablets (administered TID) in subjects with functional dyspepsia.

The study will screen approximately 700 subjects and include 564 subjects (282 subjects in both arms Test and Active control arm) and the treatment will be given as follows.

- Test group - Itopride Hydrochloride 150 mg extended release tablets once daily before any of the main meals (preferably same meal throughout the treatment)
- Active Control group - Itopride Hydrochloride 50 mg film coated tablets 3 times daily before meals

The duration of treatment will be 8 weeks and the subject follow up will be one week after the end of treatment.

In the company-sponsored studies for the efficacy and effectiveness in FD, the total planned treatment duration was 2 to 8 weeks.

The study design is chosen as non-inferiority study with statistical considerations for sample size and non-inferiority margin as described in the statistical section 10.7.

An open-label design was chosen because one tablet of Itopride Hydrochloride 150 mg extended release tablets will be compared with three tablets of Itopride Hydrochloride 50 mg film coated tablets which allows to investigate the benefit of a lower tablet intake and the preference for the treatment. Itopride hydrochloride is used for the treatment of functional dyspepsia (FD) and is currently being dosed 50 mg thrice daily. Itopride Hydrochloride 150 mg extended release once daily tablets are a strategic life cycle management opportunity. By reducing the dose to once daily instead of thrice daily, the product may improve patient compliance and adherence. This may have, in particular in subjects with FD, a beneficial effect on the outcome of the related symptomatology and disease progression.

Following multiple oral doses ranging from 50 mg to 200 mg tid, itopride hydrochloride and its metabolites showed linear pharmacokinetics over a treatment period of 7 days, with minimal accumulation. The serum concentration of the unchanged compound was found to increase very rapidly (time to reach maximum drug concentration [t_{max}]=0.5 h) after single administration of itopride, and there were good linear correlations of the C_{max} and AUC values with the dose administered. Following single oral doses of itopride hydrochloride ranging from 50 mg to 600 mg, itopride showed no relevant deviation from linear pharmacokinetics, characterized by rapid onset of absorption at approximately 1 hour and a median predominant elimination t1/2 of approximately 6–8 hours.

Subjects have to stop most drugs which are active on gastric function prior to the study. Rescue medication, i.e. PPIs or antacids, for subjects with persistent symptoms of gastric hypersecretion may be started, after confirmation by the PI, earliest after 4 weeks (visit 3). Impact of rescue medication on efficacy will be assessed in the statistical analysis.

5 SELECTION OF STUDY POPULATION

5.1 Inclusion Criteria

1. Adult male and/or non-pregnant non-lactating female subjects aged above 18 years.
2. Subjects provided written informed consent and are willing to participate in the study.
3. Subjects with functional (non-ulcer) dyspepsia according to Rome IV criteria including postprandial distress syndrome (PDS) and with or without EPS (epigastric pain syndrome) with one or more of the following:
    - bothersome postprandial fullness,
    - bothersome early satiation
    - bothersome epigastric pain,
    - bothersome epigastric burning
    - for at least 12 weeks in the preceding 6 months
4. No evidence of organic, systemic, metabolic or structural disease likely to explain symptoms - Subjects who have to undergone physical examination and lab tests (including white-cell and red-cell counts, measurement of fasting blood sugar and liver-function tests), abdominal ultrasonography, and upper GI endoscopy* in order to rule out structural cause for symptoms of FD.

    *history of upper GI endoscopy within 6 months prior to enrolment or at screening.
5. Baseline severity of at least moderate symptoms on LDQ (total score ≥ 9) at screening.
6. H. pylori negative documented test report within 3 months prior to enrolment or during screening.

5.2 Exclusion Criteria

1. Known hypersensitivity to Itopride or any component of the formulation and to any other related drug.
2. Subject with history or presence of clinically relevant evidence of cardiovascular, neurological, gastrointestinal/hepatic, renal, psychiatric, respiratory, urogenital, hematologic/immunologic, HEENT (head, ears, eyes, nose, throat), dermatological/ connective tissue, musculoskeletal, metabolic/nutritional, drug hypersensitivity, allergy, endocrine, major surgery or other relevant disease as revealed by medical history requiring treatment which at investigator's discretion might interfere with the study.
3. Subjects who cannot be treated with Itopride in line with the prescribing information.
4. Subjects scheduled for surgery during the study.
5. Subjects with a history of difficulty in swallowing.
6. Subject requiring concomitant treatment with anticholinergic drugs, drugs with narrow therapeutic index, sustained release or enteric-coated formulations.
7. Subjects taking Acid release inhibitors (e.g. histamine-2-receptor [H2]- antagonists, proton pump inhibitors [PPI], or potassium-competitive acid blockers), antacids (e.g. aluminium-

or magnesium hydroxide, sodium bicarbonate), gastric mucosa protectors (e.g. sucralfate, rebamipide).

8. Subject with history of unusual bleeding and family history for bleeding disorders.
9. Subjects with only reflux-related symptoms or who have predominantly reflux-related symptoms.
10. Subjects with esophagitis, Barrett`s esophagus, erosions or peptic ulcer disease within one year prior to the study or Zollinger-Ellison Syndrome.
11. Dyspepsia that is exclusively relieved by defecation or associated with a change in stool frequency or stool form to exclude IBS.
12. Clinically significant ECG abnormalities.
13. Subjects treated with Itopride or another gastroprokinetic within 4 weeks prior to screening.
14. Subjects who took non-steroidal anti-inflammatory drugs for more than 2 weeks prior to screening
15. Subjects with refractory FD[1](defined as FD presenting symptoms continuing for at least 6 months, unresponsive to at least two medical treatments such as PPIs, prokinetics, or H. pylori eradication) as per investigator's discretion.
16. History of or known inflammatory bowel disease (IBD) or coeliac disease.
17. History of or known severe hepatic, renal, pancreatic, cardiac, metabolic, hematological or malignant disease or trimethylaminuria.
18. Subjects with changed smoking status within the last three months.
19. History of or known GI malignancy or ulcers associated to malignancy or any alarm features for GI malignancy, e.g. GI bleeding.
20. Subjects who do not meet the criteria stated in concomitant medication section.
21. Subjects with history of severe depression, anxiety or other psychological disorders.
22. Females with child-bearing potential must agree to use an acceptable method of contraception during the study.
23. Subjects in whom an increase in gastrointestinal motility could be harmful, e.g., history of gastrointestinal hemorrhage, mechanical obstruction or perforation.
24. Specific food intolerance which is relieved by diet modifications (e.g. lactose intolerance, celiac disease).
25. Subjects with confirmed IBS as per Rome IV criteria.
26. Current alcohol or drug abuse.
27. History of abdominal surgery except appendectomy, cholecystectomy or hysterectomy, tubal ligations, bladder slings or vasectomies.
28. Hepatic cirrhosis or abnormal liver laboratory findings (defined as >3xULN of ALT or AST).
29. Subjects under hemodialysis therapy or having advanced chronic kidney disease (defined as eGFR <60 mL/min).

30. History of or known congestive heart failure NYHA class III and IV, or any other uncontrolled chronic diseases, such as: uncontrolled hypertension (systolic/diastolic blood pressure ≥160/100 mmHg); uncontrolled diabetes (HbA1c >8%).
31. Subjects currently being known to be afflicted by serious infection(s), or any known severe illness(es) which are judged by the Investigator could interfere with subjects' safety and/or study evaluation.

6 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled.

The Study Termination form in the CRF must be completed for all subjects who have entered the study (i.e. have signed Informed Consent form), including subjects dropping out prior to any study drug administration.

In case of premature termination of the subject from the study, the primary reason for this premature termination is to be indicated according to the following definitions:

- Adverse event: discontinuation due to any adverse event (AE) with a corresponding entry reflected on the Adverse Events form in the CRF.
- Lack of efficacy: the lack of expected or desired effect related to a therapy.
- Lost to follow-up: the loss or lack of continuation of a subject to follow-up.
- Withdrawal of consent: an indication that the consent to participate in the study or one or more segments of the study has been revoked.
- Protocol violation: a significant departure from processes or procedures that were required by the protocol. **Note:** subject only to be excluded from study in case of significant departure from processes or procedures that were required by the protocol and might e.g. lead to a safety issue.
- Failure to meet randomization criteria: an indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group.
- Sponsor request: an indication that the study subject was removed from the study at the sponsor's request.
- Physician decision: a position, opinion or judgment reached after consideration by a physician with reference to subject.
- Inclusion/exclusion criteria violated: eligibility criteria during screening period not met.
- Other: different than the one(s) previously specified or mentioned.

7 TREATMENTS

Study drug will only be shipped to Investigators who have provided the Sponsor (or an authorized representative) with all required study documents, including IEC/IRB approval, and have signed a final study agreement.

7.1 Treatments to Be Administered

Subjects will be randomized in a 1:1 ratio to one of the following treatment groups:

- Test group - Itopride Hydrochloride 150 mg extended release tablets once daily before one of the main meals (preferably the same meal throughout the treatment)
- Active Control group - Itopride Hydrochloride 50 mg film coated tablets 3 times daily before meals

Ganaton/Ganaton OD/Elthon/Elthon OD is the Abbott brand name for Itopride Hydrochloride in most countries and it may vary in some countries.

Itopride hydrochloride is indicated for the treatment of gastrointestinal symptoms caused by gastric dysmotility and delayed gastric emptying, like bloating sensation, early satiety, postprandial fullness, upper abdominal pain or discomfort, anorexia, heartburn, nausea and vomiting in functional (non-ulcer) dyspepsia or chronic gastritis.

7.2 Packaging and Labeling

Packaging and labeling will be controlled by Clinical Supply Management team of the Sponsor (Clinical Supplies Manager). All packaging and labeling as well as the production of study drug will be in compliance with Good Manufacturing Practices (GMP) specifications, as mentioned in the Manufacturing of Investigation and Medicinal Products Volume 4 Annex 13 and in accordance with other applicable laws or local regulations. Details on the packaging and labeling will be specified in the Packaging and Labeling Specifications and Supply Request (as applicable). Clinical supplies will be released by the quality department / prior to shipment to investigational sites. A Certificate of Analysis will be issued for the study drug. Certificate of Compliance/release, as applicable, will be issued stating the expiry date of the clinical supplies.

7.3 Storage and Dispensing of Study Drug

All clinical drug supplies are to be stored in a secure, monitored, limited-access area in accordance with labeled storage conditions, as mentioned in the IMP Instructions and Handling Manual. The Investigator will maintain accurate records of the disposition of all clinical drug supplies received during the study. These records shall include the amounts of drug supplies and the dates on which drug supplies were received from the Sponsor (or an authorized representative), dispensed to the subject, returned by the subject and returned to the Sponsor (or an authorized representative). If errors or damages in the clinical drug supply shipments occur, the Investigator must contact the Sponsor (or an authorized representative) immediately.

7.4 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to a treatment group using a centralized electronic system (interactive voice/web response system; IXRS). The IXRS assigns a fixed randomization number to each subject according to a randomization scheme. The medication will be identified using kit randomization numbers.

The randomization scheme will be provided by the study CRO/ external contractor.

7.5 Selection of Doses in the Study

Itopride hydrochloride will be given to subjects from both arms Arm 1 (Test arm) and Arm 2 (active control arm) in the following manner:

- Test group - Itopride Hydrochloride 150 mg extended release tablets once daily before one of the main meals (preferably the same meal throughout the treatment)
- Active Control group - Itopride Hydrochloride 50 mg film coated tablets 3 times daily before meals

Itopride Hydrochloride 150 mg extended release tablet once daily and Itopride Hydrochloride 50 mg film coated tablets three times a day have been reported to be well tolerated which has also been investigated in a pilot study by Kim YS et al[15].

In a study by Rai et al[16], Itopride showed effectiveness in addressing symptoms of reduced GI motility in diabetics, with improved QoL (PAGI-QoL score reduction: 13.8 ± 11.48; $P < 0.0001$). Significant improvement in the glycemic indices such as HbA1c, FPG, and PPG was also evident post-treatment, which could be attributed to the positive effects of itopride in facilitating gastric emptying, thus restoring altered kinetics of food and drug absorption.

Following multiple oral doses ranging from 50 mg to 200 mg tid, itopride hydrochloride and its metabolites showed linear pharmacokinetics over a treatment period of 7 days, with minimal accumulation. The serum concentration of the unchanged compound was found to increase very rapidly (time to reach maximum drug concentration [t_{max}]=0.5 h) after single administration of itopride, and there were good linear correlations of the C_{max} and AUC values with the dose administered. Following single oral doses of itopride hydrochloride ranging from 50 mg to 600 mg, itopride showed no relevant deviation from linear pharmacokinetics, characterized by rapid onset of absorption at approximately 1 hour and a median predominant elimination t1/2 of approximately 6–8 hours.

The first approval for itopride was in Japan, international birth date 30 June 1995, and it has been marketed under the trade name Ganaton®. Currently, Abbott's itopride is approved for treatment of GI symptoms of functional, non-ulcer dyspepsia (chronic gastritis) i.e., sensation of bloating, early satiety, upper abdominal pain or discomfort, anorexia, heartburn, nausea and vomiting in 23

countries (Argentina, Bahrain, Brunei Darussalam, Cambodia, Czech Republic, China, Egypt, India, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Myanmar, Pakistan, Philippines, Qatar, Russian Federation, Thailand, Ukraine, United Arab Emirates, Uzbekistan and Vietnam) under the major trade names Elthon®and Ganaton.

Two pharmacokinetic/biopharmaceutic studies were conducted with Itopride Hydrochloride 150 mg tablet formulation:

- ITOP-122-0212: single-dose food effect and comparative bioavailability study
- ITOP-122-0213: multiple-dose comparative bioavailability study

With these studies it was demonstrated that the Itopride Hydrochloride 150 mg tablet formulation dosed once daily under proposed label conditions (i.e. intake at 30 min before breakfast) and Itopride Hydrochloride 50 mg tablets dosed tid are bioequivalent with respect to extent of exposure to itopride. The OD formulation dosed at 30 min before a normo-caloric meal showed rapid onset of absorption with sustained release of itopride over approximately 14 h, with less peak-trough fluctuation than the IR formulation and near identical minimum plasma concentrations at the end of the dosing interval. Intake of the OD formulation following a high-fat, high-caloric meal resulted in delayed and approximately 50% higher C_{max} and 15% increased AUC without signs of dose-dumping or unexpected release characteristics, as compared to intake under fasting conditions. Intake before at 30 min before a normo-caloric meal resulted in rapid onset of absorption, and approximately 20% higher C_{max}, without affecting the extent of exposure in terms of AUC to itopride as compared to intake under fasting conditions.

After a single oral dose of the newly developed once-daily formulation, dosed at 30 min before breakfast, onset of absorption of itopride is rapid and a sustained release plasma concentration-time profile was observed up to approximately 14 h after dosing. Food has no clinically relevant effect on the extent of exposure to itopride after dosing of the once-daily formulation. Intake after a high-fat, high-caloric meal, delays and increases C_{max} (with approximately 50%) relative to intake under fasting conditions, without signs of dose-dumping. Intake of the once-daily formulation at 30 min before breakfast resulted in approximately 20% higher C_{max} as compared to intake under fasting conditions without affecting the onset of absorption of itopride or the sustained release characteristics of the formulation.

The registered dose of itopride hydrochloride for adult patients for treatment of GI symptoms caused by gastric dysmotility and delayed gastric emptying is 150 mg daily (1 IR tablet [50 mg] taken orally 3 times a day before meals). The dose may be reduced according to the patient's age and symptoms. The proposed posology for the once-daily formulation will be one tablet of 150 mg daily before one of the main meals (preferably same meal throughout the treatment; e.g. before breakfast).

The efficacy and safety of 150 mg daily Itopride hydrochloride was investigated in 19 company sponsored interventional studies in subjects with functional dyspepsia and the dose of 150 mg daily is well established.

7.6 Selection and Timing of Dose for Each Subject

Itopride Hydrochloride 150 mg extended release tablets will be given once daily before any of the main meals (preferably same meal throughout the treatment); and Itopride Hydrochloride 50 mg film coated tablets will be given 3 times daily before meals.

One tablet of 150 mg taken daily before any one of the main meals (preferably same meal throughout the treatment).

Itopride hydrochloride is rapidly and almost completely absorbed from the GI tract. Relative bioavailability is calculated to be 60% due to liver first pass metabolism. There is no effect of food on bioavailability.

Maximum drug concentration (C_{max} 0.28 µg/mL) is reached after 0.5 to 0.75 hours after administration of 50 mg of Itopride hydrochloride.

Following multiple oral doses ranging from 50 mg to 200 mg tid, Itopride hydrochloride and its metabolites showed linear pharmacokinetics over a treatment period of 7 days, with minimal accumulation.

7.7 Blinding and Treatment Code Information

This is an open-label study; blinding will not be applied. Abbott study team will remain blinded throughout the whole study until the database is locked.

7.8 Prior and Concomitant Therapy

All medication taken by the subject during the study (from signing the informed consent form through post-study follow-up) is to be recorded on the Concomitant Medication form in the CRF, except for study drug.

Forbidden Prior and Concomitant Therapy

Since Itopride has gastrokinetic effects, it could influence the absorption of concomitantly orally administered drugs. Particular caution should be taken with drugs with a narrow therapeutic index, sustained release or enteric-coated formulations. Anticholinergic drugs may reduce the action of Itopride. Prokinetics including itopride are not allowed within 4 weeks prior to screening and also not during the study (except study drug). Acid release inhibitors (e.g. histamine-2-receptor [H2]-antagonists, proton pump inhibitors [PPI], or potassium-competitive acid blockers), antacids (e.g. aluminium- or magnesium hydroxide, sodium bicarbonate), gastric mucosa protectors (e.g. sucralfate, rebamipide) are also not allowed during the study and have to be stopped 2 weeks prior to screening. Medication that may alter gastric function, including macrolide antibiotics, is not

allowed during the study and 2 weeks prior to screening. Subjects are required not to take any non-steroidal anti-inflammatory drugs during the study or 2 weeks prior to randomization. Low dose Aspirin for cardiometabolic prophylaxis up to 325 mg/day is allowed.

Subjects are allowed to take acid release inhibitors or antacids (see above) as rescue medication at earliest after 4 weeks of treatment (visit 3) in case of persistent symptoms of gastric hypersecretion based on PI clinical judgement.

Prior and Concomitant Therapy

- Treatment regimen like gastric-relevant herbal medicines can be taken if treatment started more than 1 month prior to the study and will be continued during the study in a stable dose. The same applies to anxiolytics and antidepressants: Buspirone, 5 HT1 R agonists, Mirtazapine (alpha 2 adrenergic antagonists, 5 HT 2,3 & H1 receptor antagonists), antidepressants like Amytriptyline, SSRI (e.g escitalopram), SNRI (e.g. venlafaxine). Low dose Aspirin for cardiometabolic prophylaxis up to 325 mg/day is allowed.

Dietary counselling of the subjects in scope will take place prior to randomization, e.g. avoid high fat foods, less carbonated beverages, coffee, small meals.

In case of any concerns and to accommodate any future changes in treatment guidelines or practices, the Principal Investigator may consult the Sponsor representative for concomitant medication use.

7.9 Treatment Compliance

Drug Accountability

The Investigator is accountable for all clinical drug supplies shipped to his/her study site for the duration of the study. A final accounting of the clinical drug supplies will be required at the completion/termination of the study. The Investigator is required to provide written explanation for any discrepancies.

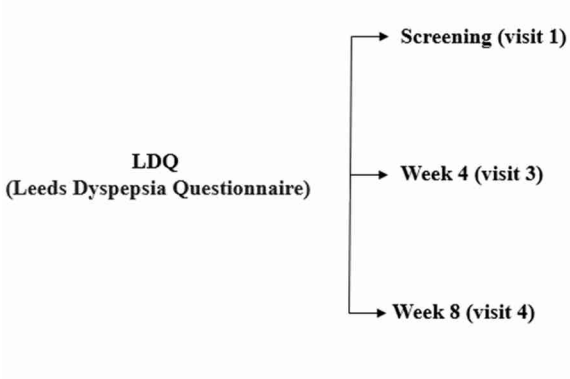
All used and unused clinical drug supplies will be inventoried and returned to the Sponsor (or an authorized representative) by a designated monitor.

The Investigator will not be permitted to return or destroy used or unused clinical drug supplies or packaging materials unless authorized by the Sponsor (or authorized representative).

8 STUDY ASSESSMENTS AND FLOW CHART

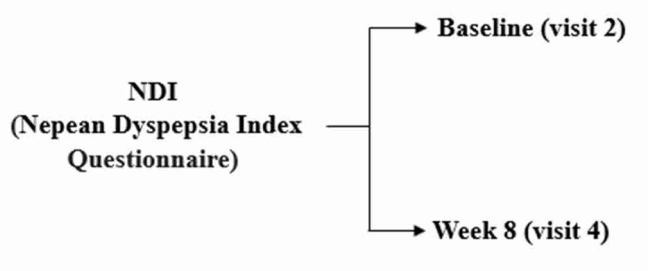
8.1 Efficacy Measurements

- **Symptoms of dyspepsia using Leeds Dyspepsia Questionnaire (LDQ)**
- LDQ Questionnaire will be completed by the site staff through interview with patient by site staff trained on administration of LDQ to capture the overall symptomatology at screening (visit 1), week 4 (visit 3) and on week 8 (visit 4). The symptoms of dyspepsia are evaluated by measuring its frequency using the LDQ questionnaire which is a fully validated instrument to assess the symptoms of dyspepsia. A dyspepsia questionnaire or Leeds Dyspepsia Questionnaire (LDQ) can identify subjects with dyspepsia by measuring its frequency and therefore will assess the severity via a calculated overall score[17-18]



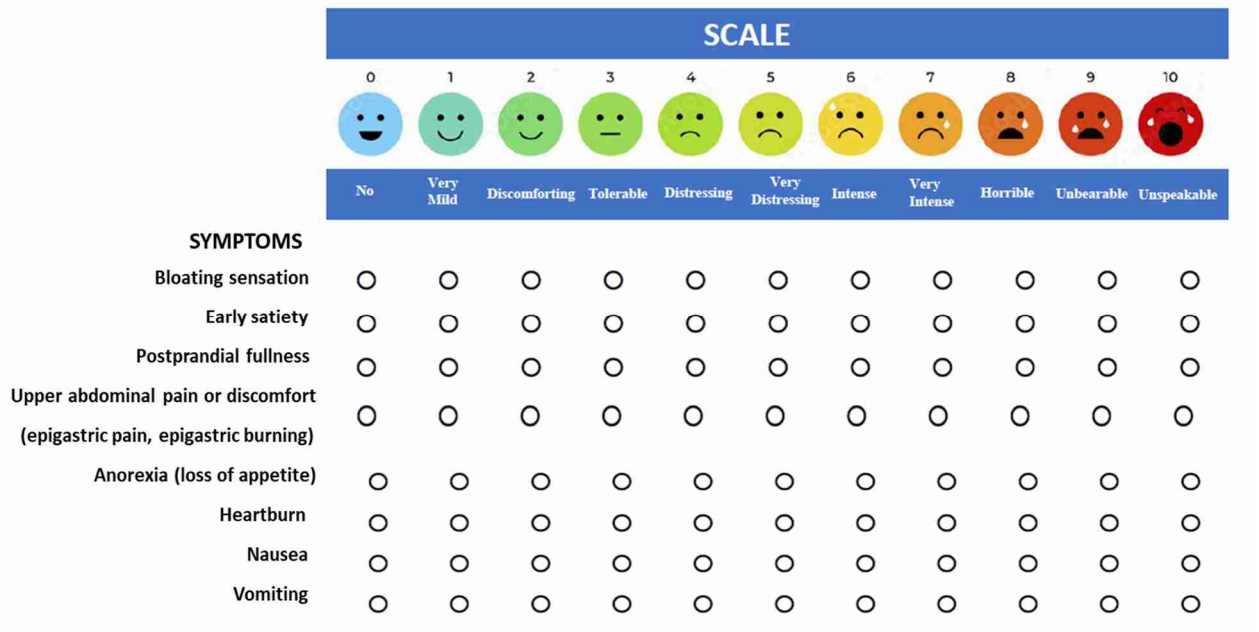
Quality of Life assessment using Short Form - Nepean Dyspepsia Index (SF-NDI)

- Quality of life is an important health outcome, which is frequently measured in various clinical and epidemiological studies. Disease can have various effects on quality of life, it depends on the area of the body afflicted and how significant that area is to the individual[19-20].
- So, evaluating items by the individual patient according to their relative importance may be helpful and beneficial. This could be a more accurate method for evaluating how a disease affects the quality of life.
- The Short Form Nepean Dyspepsia Index (SF-NDI) was designed to evaluate the impairment in each component of a subject's life as wander ability to participate and enjoy these aspects of their lives.
- Short Form Nepean Dyspepsia Index (SF-NDI) Questionnaire will be used to measure the disease-specific Quality of Life of each participant of both arms (Test and Control Arm) at baseline (visit 2) and week 8 (visit 4).



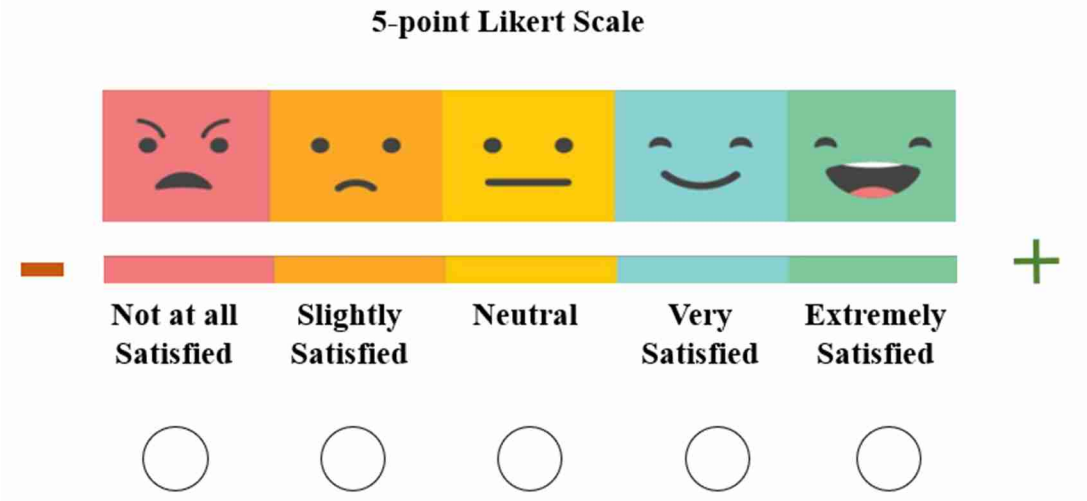
Symptoms of dyspepsia assessed by Numerical Rating Scale (NRS 11)

- The Numerical Rating Scale is widely used for self-reporting of pain intensity in clinical practices. In this study, the participants will be provided with the NRS 11 scale to mark changes for symptoms of sensation of bloating, early satiety, postprandial fullness, upper abdominal pain or discomfort (epigastric pain, epigastric burning), anorexia (loss of appetite), heartburn, nausea and vomiting at baseline and after 4 and 8 weeks of treatment[21-22].
- NRS 11 will be used to assess responders' analysis for adequate/satisfactory relief.
- NRS 11 and drug intake will be captured in patient diary. Drug intake will be recorded by the subject on a daily basis, symptoms will be recorded by the subject over the last two weeks prior to the visits. In addition, the baseline NRS 11 scores will be captured on site.



Treatment acceptance and ease of use assessed by Likert Scale

- A 5-point Likert scale is a unidimensional scale which is used to collect responders' opinions and acceptance for the provided medications[23].
- The treatment acceptance and ease of use will be assessed by subjects by answering the question "Are you satisfied with the schedule of dosing of your treatment?" using the 5-point Likert scale.
- 5-point Likert scale includes scale consisting of five points on which responders have to record their opinion to the question mentioned above.
- These five points include 1. Not at all satisfied, 2. Slightly satisfied, 3. Neutral, 4. Very satisfied, 5. Extremely satisfied.



8.2 Safety Measurements

Adverse Events

Requirements for collecting, recording and reporting of AEs are described in Section 9. Each subject is to be evaluated at the termination visit. Should any AE be identified at this visit, the Investigator will continue to follow the subject as described in Section 9.1.2.

Safety Laboratory data will be collected for the determination of the following parameters:

Laboratory evaluation:

The following laboratory parameters will be evaluated:

1. Hematology –
   Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, platelet count, and differential blood count (only if indicated)
2. Biochemistry -

Random blood sugar, liver function tests [serum bilirubin, alkaline phosphatase, ALT (alanine amino transferase), AST (aspartate amino transferase), LDH (lactate dehydrogenase), gamma-glutamyl transferase], calcium, potassium, Serum Prolactin (Fasting), Serum Lipase (only baseline)

For all laboratory parameters with values outside the normal range (or abnormal results), the clinical significance will be judged by the Investigator.

Vital Signs

Height will be recorded at screening only and weight will be recorded at all visits.

Body temperature, pulse rate, respiration rate, blood pressure, will be recorded at baseline and at every visit during the study period.

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate are to be measured while the subject is in sitting position after 5 minutes rest.

12-Lead Electrocardiogram (ECG)

A 12-lead ECG must be recorded while the subject is in supine position after 5 minutes rest at screening.

The ECG should be interpreted by the Investigator (normal/abnormal). For abnormal ECGs the clinical significance (yes/no) should be judged by the Investigator and the abnormality is to be specified. These subjects with clinically significant ECG abnormalities will not be included into the study.

Physical Examination

A physical examination should be performed and any relevant findings are to be recorded on the Medical History form in the CRF (for findings from the past that occurred prior to screening visit), or on the Adverse Event form in the CRF for findings presently occurring. This will be done at visit 1, 2, 3 and 4.

Pregnancy test

Urine pregnancy test (dipstick) will be done in all female subjects of child-bearing potential at the time of screening, to rule out pregnancy (if not postmenopausal or following tubal ligation or hysterectomy).

8.3 Other Assessments

Informed Consent

Voluntary written informed consent must be obtained from each subject (or their legally acceptable representative) prior to performing any study-related procedures (see Section 1.3).

Demographic Data

Demographic data (gender, age, race) will be collected for all subjects.

Medical History

Any clinical event, including diagnosis, condition, or surgery, that occurred prior to the screening visit (before the informed consent is signed), is to be recorded on the Medical History form in the eCRF. In case a clinical event concerns a chronic disorder, which means it started in the past and it is still present at the screening visit, it should also be recorded on the Medical History Form in the eCRF. Examples of these events are diabetes, migraine, and hay fever (documentation of pregnancy, see section 9.3).

Concomitant Medication

All medication taken by the subject during the study (from signing the informed consent form through post-study follow-up) is to be recorded on the Concomitant Medication form in the eCRF, except for study drug.

Compliance and treatment adherence

The information about drug intake/adherence and NRS 11 self-reporting of symptoms will be captured in Patient diary. Drug intake will be recorded by the subject on a daily basis, symptoms will be recorded by the subject over the last two weeks prior to the visits. In addition, the baseline NRS 11 scores will be captured on site.

8.4 Appropriateness of Measurements

All measurements will be performed using standard methods which are generally recognized as being reliable, accurate, and relevant.

8.5 Primary Efficacy Variable(s)

The change in the overall severity of functional dyspepsia between baseline and week 8, as measured by the Leeds Dyspepsia Questionnaire (LDQ) severity score has been selected as primary endpoint.

LDQ is a useful tool for assessing the presence and severity of dyspepsia. In a study by Moayyedi et al.[17], the LDQ had a high degree of sensitivity in detecting dyspepsia compared to the opinion of a gastroenterologist or a General Physician as the gold standard. LDQ questionnaire is validated in primary and secondary care populations and hence is suitable for general practice dyspepsia studies.

Holtmann et al.[2] investigated this parameter with Itopride in a placebo-controlled study. Other studies have used LDQ for FD as primary endpoint.

8.6 Flow Chart of Study Assessments

All study assessments will be conducted as indicated in Table 2, which displays the frequency and timing of all measurements.

Table 2: Study Assessments

Periods	**Screening period**	**Treatment period**			**Follow up**
Visits (V)	**V1**	**V2**	**V3**	**V4 (ET/ED)**	**TC**
Week			***W4***	***W8***	
Day	***Day -1***	***Day 1***	***Day 29***	***Day 57***	***Day 64***
Visit window	***-14 to -1 days***		***±1 day***	***±1 day***	***+1 day***
Informed Consent	X				
Demographic data	X				
Medical history	X				
Inclusion/Exclusion criteria	X	X			
Physical examination	X	X	X	X	
Weight, Height (screening only), BMI[5]	X	X	X	X	
Vital signs	X	X	X	X	
Hematology	X			X	
Biochemistry (including RBS, Serum prolactin (fasting), Serum lipase[7])	X			X	
Pregnancy test[1]	X				
Test report for H. pylori[2]	X				
Upper GI Ultrasound	X				
Endoscopy[3]	X				
ECG	X				
Randomization		X			
Leeds Dyspepsia Questionnaire (LDQ)	X		X	X	
Short From Nepean Dyspepsia Index (SF-NDI) questionnaire		X		X	

NRS 11 onsite (baseline only)		X			
Patient diary distribution		X	X		
NRS 11 recorded in patient diary[4]		X	X		
Dispense Study drug		X	X		
Drug intake recorded in patient diary[6]		X	X		
Diary return			X	X	
Study drug return			X	X	
Study drug accountability and adherence assessment			X	X	
Adverse events	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Treatment acceptance and ease of use assessment using Likert scale				X	

ET – End of treatment, ED – Early discontinuation, TC – Telephone contact, D – day, V – Visit

1. For women of child-bearing potential (including those without history of surgical sterilization and women with <2 years post-menopause)
2. H. pylori test report in medical history within 3 months before randomization, otherwise to be performed during screening.
3. Endoscopy in medical history within 6 months before randomization, otherwise to be performed during screening.
4. Symptoms will be recorded by the subject over the last 2 weeks prior to the next visit.
5. Will be calculated during analysis, not by investigator.
6. Will be recorded daily.
7. Serum Lipase at V1 (baseline) only.

9 ADVERSE EVENTS

The reference safety information (RSI) used for both IMP and the comparator is the current Investigator brochure Itopride.

9.1 Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom (including an AE occurring from drug abuse, an AE occurring from drug withdrawal and any AE occurring from failure of expected pharmacological action), or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

9.1.1 Recording of Adverse Events

Any AE should be recorded on the Adverse Events form in the CRF and source documents. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should group together into a single term signs and symptoms which constitute a single diagnosis.

The existence of or change in an AE may be concluded due to the necessity to administer a concomitant medication, from a spontaneous report of the subject, from the physical examination or from special tests like ECG, EEGs, laboratory assessments or other study specified tests (source of AE).

AE collection period is defined as any time after informed consent is obtained until 30 days after the last day of study participation.

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken with study drug, the concomitant medication given and the outcome as well as whether the event led to study termination will also be recorded.

<u>Severity</u>

The severity of the AE should be characterized as "mild, moderate or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity.

Drug-Event Relationship

The causal relationship between the study drug and the AE should be characterized according to the following:

- Unrelated – there is not a reasonable possibility that the study drug caused the AE.
- Unlikely – suggests that only a remote connection exists between the study drug and the event. Other conditions, including concurrent illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the AE.
- Possible – suggests that the association of the AE with the study drug is unknown, however the event is not reasonably supported by other conditions.
- Probable – suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of the disease state, or concomitant medication reactions) do not appear to explain the AE.
- Certain - clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals.

Outcome

The outcome of the adverse event should be classified according to the following definitions:

- Recovered / resolved: the event has resolved (no further symptoms are present and no treatment is being received by the subject).
- Recovered / resolved with sequelae: the event has resolved but there may be lingering effects present (e.g., a scar following a cut or abrasion).
- Fatal: the subject died as a result of the event. This code should only be used for the event that caused the death, not any event that was present at the time of the subject's death. Fatal events require immediately reporting to the Sponsor (or an authorized representative).
- Unknown: may only be used in the event that the subject is lost to follow-up and no reliable data can be obtained.
- Not resolved: the event is not yet resolved and is ongoing.

All efforts should be made to classify the AE according to the above categories.

9.1.2 Follow-up of Adverse Events

All AEs occurring during the study are to be followed up in accordance with good medical practice until resolved or judged no longer clinically significant, or if a chronic condition, until fully characterized. All follow-up results are to be reported to the Sponsor (or an authorized representative).

9.2 Serious Adverse Events (SAEs)

Definitions of Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of an existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is any suspected transmission via a medicinal product of an infectious agent,
- is considered an important medical event (an event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse as well as spontaneous or elective abortions, stillbirths and ectopic pregnancies).

9.2.1 Reporting Serious Adverse Events

Any SAE (fatal or life-threatening SAE and other SAEs), whether or not related to the study drug, must be reported immediately within 24 hours of the investigator's awareness of the event by telephone and/or emailing the appropriate SAE forms to the Sponsor (or an authorized representative).

Email: safety.ganaton@tech-observer.com
Contact (toll-free): +13054400254

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9.3 Pregnancy

If a subject should become pregnant during the study, the event will be reported on the Pregnancy Form within 1 day of the investigator's knowledge of the pregnancy. The Pregnancy Form is to be fax or email to the Sponsor (or an authorized representative) at the contact numbers listed in Section 9.2.1.

If pregnancy occurs in a subject from the time of ICF signature who does not qualify for allocation to treatment, i.e. Screen Failure, the pregnancy should be recorded in patient's medical file only, in accordance to local requirements. The pregnancy related medical status change information will not be reviewed by Abbott or delegated staff. The pregnancy will not qualify as a study (S)AE.

If pregnancy occurs in a subject from the time of ICF signature who is not dis-qualified for allocation to treatment, the pregnancy should be recorded in patient's medical file in accordance to local requirements and in Abbott's pregnancy from. The pregnancy related medical status change information will be reviewed by Abbott or delegated staff. The pregnancy will not qualify as a study (S)AE.

The pregnancy evolution and outcome, i.e., the health status of the newborn, is to be reported on the Pregnancy Outcome Form and reported to the Sponsor (or an authorized representative) within 1 day of the investigator's knowledge of the event.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth, ectopic pregnancy or congenital anomaly is considered a SAE and must be reported to the Sponsor (or an authorized representative) within 24 hours of the investigator becoming aware of the event and followed-up as described in Section 9.1.2.

10 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Data handling will be the responsibility of the Clinical Data Management (CDM) team of the CRO. The data will be inspected for inconsistencies by performing validation checks. Any inconsistencies found will be resolved by the monitor after contacting the Investigator. When the data in the database are considered clean and the subjects allocated to subject samples in a blind data review, the database will be locked to prevent unauthorized access. Next, the database will be made available as SAS® files for statistical analysis.

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the Statistical Analysis Plan prepared by Biostatistics projects Planning and Programming (BPP) team of the CRO and approved by Abbott before database lock.

The statistical analysis will be performed by the BPP team of the CRO.

10.1 General Definitions and Conventions

Time-Related Definitions

All assessment dates will be related to the first day of study drug administration. This first day of drug administration is referred to as Day 1. Day –1 is the day that is preceding Day 1 and a Day 0 will not be defined.

The baseline period will be defined as the period from informed consent to the first study drug administration. The baseline value for a variable is defined as the last non-missing value collected before first study drug administration.

The endpoint value for efficacy variables is defined as the last non-missing value assigned to treatment for the subject.

All variables planned to be measured at one or more time points and supposed to be time-related will be windowed.

Coding Systems

AEs and medical history Investigator terms will be assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and primary system organ class (SOC) according to the MedDRA (applicable version will be captured in Data Management Plan) thesaurus.

Concomitant medications will be classified according to active drug substance using the WHO drug dictionary. The generic name, the preferred name and the WHO name will be assigned.

In addition, the Anatomical Therapeutic Chemical (ATC) classes will be assigned to the drug ID. ATC codes are defined to the 4th level. For each medication, the primary ATC class will be assigned manually based on the generic name and the reason for use.

Default Summary Statistics

The default summary statistics for quantitative and ordinal variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) for subjects with data. Any other summary statistics will be described on an individual basis.

Default Frequency Tabulations

For qualitative variables, per category the numbers and frequencies of subjects with non-missing data (n, %) will be the default summary presentation, and if appropriate and present, the number of missing values.

For AEs, medical history and concomitant medications, however, the denominator for the percentage calculation will be the number of subjects at risk for the particular treatment arm. A subject will be considered at risk if the subject is in the safety sample and entered the respective study period.

Subject Listings

Individual subject listings will be produced for all raw data and a selection of the derived data.

10.2 Subject Samples

The main subject samples of interest are defined as follows.

The all subjects consented sample will consist of all subjects who:

- Gave their informed consent.

The all subjects randomized to treatment sample will consist of all subjects who:

- Were in the all subjects consented sample; and
- Were randomized to treatment.

The safety sample will consist of all subjects who:

- Were in the all subjects allocated to treatment sample; and
- Had at least one dose of study medication administered.

The full analysis (FA) sample will consist of all subjects who:
- Were included in the safety sample; and
- Had data for at least one post-baseline assessment of any efficacy measurement.

The per-protocol (PP) sample will be defined through blind data review and will consist of all subjects who:
- Were included in the FA sample; and
  Did not present any major protocol violation.

Efficacy

Primary efficacy:

- An ANCOVA analysis will be performed with the change in the LDQ score as dependent variable and treatment group, site and LDQ baseline value as additional factors. The difference between the two treatment groups will be calculated for the non-inferiority comparisons, together with a two-sided 95% confidence interval. Non-inferiority will be considered achieved if the lower bound of the 95% confidence interval of the difference

between the two groups is greater than 1.75 (NI-margin). Normal approximation will be assumed for the parametric analyses. The primary analysis will be performed for both the per protocol set and the full analysis set. The analysis for the per-protocol set will be regarded as primary.

Secondary efficacy:

- Full analysis sample will be used for the analysis of the secondary endpoints.
- All secondary efficacy variables will be assessed using descriptive statistics.
- In addition, the change from baseline in LDQ score at week 4 and the NRS 11 score for each symptom will be evaluated using the same analysis as specified for the primary endpoint.
- Impact of rescue medication on efficacy and safety will be investigated by appropriate statistical methods like e.g. imputation methods depending on the number of subjects needing rescue medication. In addition subgroup analyses will be performed as well

10.3 Safety

The safety sample will be used for the analysis of the safety and tolerability data.

An AE that starts during a unique treatment or that already exists before the start of that unique treatment but worsens during the treatment, will be considered as treatment emergent for that unique treatment.

For the definition of treatment emergent, the following unique treatments are distinguished by applicable study period:

- Itopride Hydrochloride 150 mg extended release tablets
- Itopride Hydrochloride 50 mg film coated tablets

AEs will be reported on a per-subject basis, i.e. counting subjects rather than events. This means that if a subject suffers the same AEs repeatedly during the applicable study period, the event will be counted only once for that period. Repeated events per subject will be summarized according to the following rule: if a subject suffered the same AE more than once, the event will be assigned the worst severity, the closest relationship to the study drug and the earliest starting date. Only treatment emergent AEs will be reported. In the listings, however, all occurrences of the AEs will be presented.

For each unique treatment, treatment emergent AEs will be summarized per primary SOC, per HLT by primary SOC and per PT by HLT and primary SOC. Severity and drug-event relationship of treatment emergent AEs are summarized separately.

Vitals signs, including changes from baseline will be summarized. A frequency table will be presented for markedly abnormal values.

Laboratory variables, including changes from baseline will be summarized. A frequency table will be presented for markedly abnormal values. Shift tables will be presented according to the reference ranges (low, normal or high).

10.4 Other Assessments

The assignment of subjects to subject samples, the disposition of subjects with respect to premature termination, reason for premature termination, drug exposure and treatment compliance will be summarized per treatment group.

Demographics and other baseline characteristics will be summarized per treatment group.

Medical history, including coding data will be summarized per primary SOC, per HLT by primary SOC and per PT by HLT and primary SOC.

Major protocol deviations will be listed.

Concomitant medication, including coding data will be summarized per assigned treatment period for incidence per subject, for primary therapeutic subgroup (3rd level ATC code) and for generic name by therapeutic subgroup.

10.5 Subgroup Analysis

Subgroup analyses by geographical regions will be performed. Key efficacy and safety results will be summarized across subgroups defined by geographical regions (country, gender and age).

10.6 Interim Analysis

For this study, no interim analysis is planned.

10.7 Determination of Sample Size

Assumptions for sample size calculation are based on the studies of Holtmann et al.[2] and Talley et al.[3] from which a standard deviation of 7 can be assumed for the change of the LD questionnaire.

For the NI margin following assumptions were made:

- In the Holtmann study[2] a difference to placebo 2 (95% CI: 0.03-3.97) in the LDQ was reported.
- In the Ang[4] publication (2011) a difference of 10-15% to placebo is regarded as clinically relevant
- NI-margin needs to be lower than 2. A difference of 15% results in 1.74. Therefore, a NI margin of 1.75 is chosen.

Assuming a NI margin of 1.75 and standard deviation of 7 for the change in the LDQ severity score, 253 subjects per treatment arm are required to conclude non-inferiority between the 2 treatment groups with a power of 80% at α-level of 2.5% single sided. Adding a 10% drop-out rate the total sample size would be 564 subjects (N= 282 per arm).

11 INVESTIGATOR OBLIGATIONS

The Investigator agrees to conduct the clinical study in compliance with this protocol which was approved by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

11.1 Essential Study Documents

The Investigator is responsible for providing and maintaining essential study documents. Essential study documents are those documents that individually and collectively permit the evaluation of the conduct of the study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator and the Sponsor (or an authorized representative) with the standards of GCPs and with all applicable national regulatory requirements.

Essential study documents will include regulatory documents as well as source documents which are original documents, data and records of clinical findings, observations and other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source documents will include hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratories and at medical/technical departments involved in the clinical study.

The Investigator agrees to allow direct access to all essential clinical study documents for the purpose of monitoring and/or auditing by the Sponsor (or an authorized representative) and inspection by the appropriate national and foreign regulatory authorities.

11.2 Case Report Form (CRF) Completion

Data reflecting the subject's participation with the study drug under investigation will be reported to the Sponsor (or an authorized representative). The data will be recorded on the designated (e)CRFs provided or approved by the Sponsor.

The (e)CRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed (e)CRF for each subject who did not fail screening. All supportive documentation submitted with the (e)CRF, such as laboratory or hospital records, should be clearly identified with

the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

All data must be entered in English. The (e)CRFs should always reflect the latest observations on the subjects participating in the trial. Therefore, the (e)CRFs are to be completed as soon as possible after the subject's eligibility has been confirmed and thereafter during or after the subject's visit. To avoid inter observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the (e)CRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the (e)CRF. The Investigator will be required to (electronically) sign off on the clinical data.

The monitor will review the (e)CRFs and evaluate them for completeness and consistency. The (e)CRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor is not allowed to enter data in the (e)CRFs.

If additional corrections are needed, the responsible monitor or Data Manager will raise a query. The appropriate investigational staff will answer queries sent to the Investigator.

For each subject that has signed the informed consent but does not qualify for allocation to treatment, i.e. Screen Failure, only the following information is required to be collected

- Date of Informed Consent
- Demographics
- Reason for Screen Failure
- Inclusion / Exclusion Criteria Violated
- SAEs

In case other data for screen failures is entered in the (e)CRF, these data should be clearly indicated in the raw datasets and removed from the analysis datasets.

EDC:

Electronic Data Capture (EDC) will be used for this trial, meaning that all CRF data will be entered in electronic forms at the investigational site. Data collection will be completed by authorized study site personnel designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the system for any study subjects. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance.

Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Also, the queries and resolutions

will be audit trailed by the EDC application meaning that the name of investigational staff, Data Manager and Monitor, time and date stamp are captured.

eCRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

11.3 Essential Records Retention

The Investigator should maintain the essential clinical study documents (including CRFs, source documents, clinical drug disposition records, signed subject informed consent forms, AE reports and other regulatory documents) as required by the applicable national regulatory requirements. The Investigator is to take adequate measures to prevent accidental or premature destruction of these documents. In the event of accidental destruction, the Investigator should notify the Sponsor (or an authorized representative) immediately.

Essential clinical study documents will be retained at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region OR at least two (2) years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents shall be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor (or an authorized representative).

The Investigator is required to notify the Sponsor (or an authorized representative) prior to changing the location or status of any essential clinical study documents. The Sponsor (or an authorized representative) will be responsible for informing the Investigator as to when these documents no longer need to be retained.

11.4 Investigator Agreement

The Investigator is responsible for assuring the proper implementation and conduct of the clinical study including those study-related duties delegated to other appropriately qualified individuals. The Investigator and his/her staff will cooperate with the Sponsor (or an authorized representative) during monitoring and auditing visits to assist with the review of the study data and resolve any discrepancies.

The Investigator will demonstrate due diligence in recruitment and screening of potential study subjects. The enrollment rate should be sufficient to complete the study as agreed with the Sponsor (or an authorized representative). The Sponsor (or an authorized representative) is to be notified of any projected delays, which may impact the completion of the study.

The Sponsor retains the right to terminate the clinical study at any time for any reason. In such an event, instructions on the requirements for the discontinuation of subjects will be provided by the Sponsor (or an authorized representative).

12 SPONSOR OBLIGATIONS

12.1 Protocol Amendments

Only the Sponsor (or an authorized representative) will make modifications to the clinical study protocol, which will be documented in a written amendment that describes all changes that will be implemented. Protocol amendments will be categorized as either substantial or non-substantial.

Protocol amendments will be considered substantial when the changes have significant impact on:

- The safety of physical or mental integrity of the subjects
- The scientific value of the study
- The conduct or management of the study
- The quality or safety of any investigational medicinal product or control used in the study

Protocol amendments will be considered non-substantial when the changes affect only administrative issues with the conduct of the study, i.e., changes in telephone numbers or addresses.

The Sponsor (or an authorized representative) will be responsible for notifying the appropriate national regulatory authorities in writing of any amendments to the protocol prior to the changes being implemented except in those cases where the changes are necessary to eliminate an immediate hazard to the clinical study subjects.

Substantial amendments will require written approval by the IEC/IRB prior to being implemented by the Investigator at the study site except under those circumstances described previously. Non-substantial amendments will not require approval by the IEC/IRB unless requested by the IEC/IRB.

12.2 Study Monitoring

The study will be monitored by authorized representatives of the Sponsor throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence). Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study.

In addition to onsite monitoring the Sponsor may choose a combination of on-site and centralized monitoring. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

These visits will be conducted to evaluate the progress of the study, ensure the rights and well-being of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments, GCPs and applicable national regulatory

requirements. A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

12.3 Quality Assurance and Quality Control

As part of the Sponsor's (or an authorized representative's) quality management approach, Quality Assurance department may conduct on-site audits of all aspects of the clinical study either during the study or after the study has been completed.

The clinical study may also be subject to inspection by regulatory authorities (national or foreign) as well as the IECs/IRBs to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCPs, as well as the applicable regulatory requirements.

13 PUBLICATION POLICY

The data generated by this study are confidential information of the Sponsor. The Sponsor will publicly disclose the study and the study results of all applicable clinical trials following legal and regulatory requirements. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

14 INSURANCE

The Sponsor has taken out a liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines whichever is applicable. Insurance will be covered by the sponsor in accordance to the local regulations.

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16 APPENDICES

16.1 Appendix – Participating Countries' National Insurance Requirements

Insurance will be covered by the sponsor in accordance to the local regulations

16.2 Appendix – Medical expert for the trial.

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16.3 Appendix –Clinical laboratory(ies) involved in the trial

The respective local clinical laboratories will be used after site selection.