Klinik Arlesheim

Perceived Changes in Symptom Burden and physiological effects of a proprietary phyto-therapeutic preparation (Amara) in patients with functional dyspepsia: Prospective study as Investigator Initiated Trial (IIT)

Deutsch:

Subjektive Veränderungen der Symptombelastung und physiologische Wirkungen eines proprietären Phytotherapeutikums (Amara Tropfen) bei Patienten mit funktioneller Dyspepsie (Reizmagensyndrom): „Eine prospektive, Prüfer-initiierte Studie (IIT)“

Short title: Amara-Tropfen beim Reizmagensyndrom

Study Type:	Intervention Study as an Investigator-Initiated Trial (IIT), Phase IV
Study Categorisation:	Risk category according to HRA: A
Study Registration:	Clinicaltrials.gov ID: NCT05553587
Study Identifier:	Amara-KLA-01-22
Sponsor, Sponsor-Investigator or Principal Investigator:	Prof Dr med Mark Fox Facharzt für Gastroenterologie und Innere Medizin Leitender Arzt, Zentrum für Integrative Gastroenterologie Leiter, Magen Darm Funktion: Basel, Labor und Klinik für funktionelle Magendarm Erkrankungen und Motilitätsstörungen Klinik Arlesheim, Pfeffingerhof 1, 4144 Arlesheim Tel. +41 (0)76 3580379 mark.fox@klinik-arlesheim.ch
Investigational Product:	Amara drops “a balanced mixture of medicinal plants with tonic and aromatic bitter substances, suitable for stimulating digestion”
Protocol Version and Date:	Version 1.4 10.11.2023

Version control

Version Nr	Version date	Modified without version change	Protocol Description, comments	Control
1.0	22.03.2022		Original version in English.	MF
1.0	16.04.2022		Updated to include minor edits requested by collaborators	MF
1.1	16.06.2022		Updated to address minor issues raised by ethics commission	MF
1.3	14.09.2023		Inclusion criteria modified to improve recruitment and updated to address minor issues requested by collaborators	
1.4	10.11.2023		Addition of further, non-invasive physiological measurements, specifically gastric electrical activity acquired by the Gastric Alimetry System (High Resolution Gastric Mapping / Electro-gastrography). Concurrent measurement of heart rate will also be obtained Inclusion criteria modified / clarified in regard to assessment of dyspeptic symptoms by the LDQ and psychological state by HADS. Timeline of study extended to September 2024	

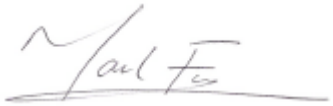
SIGNATURE PAGE

Study number Amara-KLA-01-22

StudyTitle Perceived Changes in Symptom Burden and physiological effects of a proprietary phyto-therapeutic preparation (Amara) in patients with functional dyspepsia: Prospective study as Investigator Initiated Trial (IIT)

The Sponsor-investigator has approved the protocol version (V1.3 14.09.2023) and confirm hereby to conduct the study according to the protocol, current version of the World Health Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator: Prof. Dr. med. Mark Fox



14.09.2023

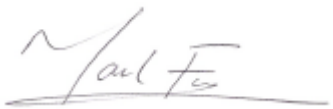
Place/Date Signature

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Health Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Site: Klinik Arlesheim, Pfeffingerhof 1, 4144 Arlesheim

Principal Investigator: Prof. Dr. med. Mark Fox



14.09.2023

Place/Date Signature

TABLE OF CONTENTS

STUDY SYNOPSIS

Sponsor-Investigator	Prof. Dr. med. Mark Fox Leitender Arzt, Zentrum für Integrative Gastroenterologie Leiter, Magen Darm Funktion: Basel, Labor und Klinik für funktionelle Magendarm Erkrankungen und Motilitätsstörungen
Study Title:	Perceived Changes in Symptom Burden and physiological effects of a proprietary phyto-therapeutic preparation (Amara) in patients with functional dyspepsia: Prospective study as Investigator Initiated Trial (IIT)
Short Title / Study ID:	Amara bei Dyspepsie, Amara-KLA-01-22
Protocol Version and Date:	Version 1.4, 10.11.2023
Trial registration:	Clinicaltrials.gov ID: NCT05553587
Study category and Rationale	Risk category A acc. to ordinance HRO Art.7 The investigational drug is approved with a reduced dossier without indication according to Art. 25 para. 1 KPAV (SR 812.212.24). This study follows the indication text licensed by Swissmedic: "… Weleda Amara-Drops can be used for digestive complaints such as heartburn, flatulence and bloating after meals, to stimulate the bile flow and for loss of appetite and nausea. The effect of Weleda Amara drops is based on a balanced mixture of medicinal plants with tonic (invigorating) and aromatic bitter substances, which are suitable for stimulating digestion." Further, no side effects have been reported in past studies so far. All these reasons lead us to the conclusion that this study is only associated with minimal risks and should be classified in risk category A.
Clinical Phase:	Confirmatory Trial (Phase IV)
Background and Rationale:	Functional dyspepsia (FD) with postprandial distress is a common functional gastrointestinal (GI) disorder characterized by the occurrence of epigastric symptoms such as early satiety (fullness), nausea and upper abdominal pain after meals at least twice a week over at least six months (Rome IV criteria). By definition, no structural disease is found on routine endoscopy or imaging studies. Instead, symptoms are thought to be related to abnormal gastrointestinal motility (e.g., impaired gastric relaxation, abnormal emptying) and increased sensitivity to gastric distension and the digestive process. Additionally, detailed studies of the mucosa often reveal low-grade inflammation in the duodenum and hyperpermeability ("leaky gut"). Epidemiological studies report a 10-30% prevalence of functional dyspepsia (FD) worldwide. When dyspeptic symptoms are short in duration and relatively mild, many patients wish to self-manage with dietary adaptation and /or over the counter (OTC) preparations. Others report high rates of intolerance to prescription medications. In these patients complementary and alternative medicines (CAM) based on natural products, such as plant-based "phytotherapy", are particularly appealing. Several herbal therapies for functional dyspepsia have been tested in randomized clinical studies. These include phytochemicals such as peppermint oil that inhibits smooth muscle contraction by direct blockade of calcium channels and other effects, deglycyrrhizinated licorice that increases gastric mucus secretion and may enhance mucosal protection and other preparations that combine multiple herbal products with the intention of inducing synergistic effects that promote normal digestive function. In particular, STW-5 (Iberogast©, Bayer) has

	been shown to have physiological effects on gastric accommodation and contractility. A double-blind non-inferiority randomized control trial (RCT) comparing Iberogast to cisapride (5-HT4 agonist) showed equal effectiveness for both medications. More recently, a meta-analysis of 3 double blind RCTs provided evidence that Iberogast is more effective than placebo to improve dyspeptic symptoms. Amara tincture (Weleda, Arlesheim, Switzerland) is a proprietary preparation used for many decades in complementary medicine that is marketed for the treatment of functional digestive disorders. Patients take 10-20 drops before meals to relieve loss of appetite, bloating, nausea, and other dyspeptic symptoms. These bitter substances are thought to promote digestion and relieve symptoms by stimulating the secretion of gastric and pancreatic enzymes, upper gastrointestinal motility and gastric emptying. These prokinetic effects may be therapeutic in patients with functional dyspepsia because there is an association between optimally measured delayed gastric emptying (GE) and upper gastrointestinal symptoms. To date, the effect of Amara has not been subjected to pre-clinical or clinical studies. The primary aim of this investigator-initiated, prospective, open-label therapeutic study is to assess perceived changes in symptom burden reported by patients with functional dyspepsia treated with Amara. Additionally, the physiological effects of Amara on gastric motor and sensory function will be assessed using validated methods.
Protocol Summary	A prospective, open label, non-randomized study will assess (i) Perceived changes in symptom burden reported by patients during regular intake of 10-20 Amara Drops before main meals using the validated Leuven Dyspepsia Score. (ii) Physiological effects of 20 drops Amara tincture on gastric emptying using the 400ml Nottingham Test Meal with non-radioactive ^{13}C-acetate breath test and concurrent assessment of filling sensation and dyspeptic symptoms by Visual Analogue Scores (VAS). (iii) In a subset of 20 consecutive patients, the 13C-acetate breath test will be combined with measurements of gastric electrical activity acquired by the Gastric Alimetry System (High Resolution Gastric Mapping / Electro-gastrography). At the same time heart rate monitoring will be obtained. Individuals that fulfill the diagnostic criteria for functional dyspepsia with postprandial distress syndrome according to the Rome IV criteria will be recruited. At the first study visit (Study Visit #1), Symptom questionnaires and other questionnaires to assess general gastroenterological health and psychiatric well-being will be completed at the time of recruitment. The questionnaires will be sent via e-mail to a patient. The e-mail contains a secure link to the questionnaires. The questionnaires will be filled in on a patient's smartphone Additionally, the Lüscher Color Test (LCT) will be performed. This non-verbal, non-written test has been developed to assess patient's personality and psychiatric state. This could be of interest in patients with disorders of brain-gut interaction that may not admit to the role of central factors in their illness. Eligible patients will have no clinically relevant medical co-morbidity or previous major gastrointestinal surgery (appendectomy, hysterectomy, cholecystectomy, hernia repair are not exclusion criteria) and must have had a normal upper gastrointestinal pan-endoscopy in the previous 3 years. If not known, Helicobacter pylori status will be assessed by ^{13}C-stool antigen test (endoscopy not required). Gastric function will be assessed by ^{13}C-breath test measurements with concurrent measurements of visceral sensitivity. A 2-4 week run-in period follows

	the first study visit (no new treatments during this period). The presence and severity of dyspeptic symptoms will be reported every day using an on-line application downloaded on the patient's smart phone (an electronic reminder will be sent at 21:00 every day). The LCT will be repeated during the second study visit (Study Visit #2), At this time, gastric function will be assessed by ^{13}C-breath test measurements with concurrent high-resolution electro-gastrography (Gastric Alimetry System) and heart rate monitoring plus assessment of visceral sensitivity after ingestion of a validated 400ml liquid "Nottingham Test Meal (NTM)". Amara Drops will be dispensed with 10-20 drops (0.25-0.50ml) taken three times a day prior to meals for 4 weeks. Patients are free to vary the dose between these limits as considered appropriate. The amount taken will be monitored by checking the volume remaining in the bottle at the end of the 4-week intervention. During this time, patients will continue reporting the presence and severity of dyspeptic symptoms and any side effects into the app. At the end of the study period (Study Visit #3) the questionnaires including LCT and the ^{13}C-breath test measurement with concurrent high-resolution electro-gastrography (Gastric Alimetry System) and heart rate monitoring plus concurrent assessment of visceral sensitivity will be repeated. Additionally, the patients will be asked if their global satisfaction was better on Amara treatment, whether they wish to continue treatment and /or recommend the treatment to others with similar symptoms. Questionnaires and diary entries on side effects are also available as paper version.
Risk / Benefit Assessment	The initial assessment of patients with functional dyspepsia will adhere to international guidelines on the investigation of this condition. Amara Drops (Weleda) is a proprietary preparation that has been marketed over the counter (OTC) for many years. No serious side effects have been reported. ^{13}C-breath test gastric emptying studies and other measurements of gastric function (e.g. electro-gastrography) are indicated in patients with functional dyspepsia that do not respond to first-line, dietary management, and empirical treatment. These tests are non-invasive and not radioactive and is associated with no adverse outcomes. Clinical validation studies report that the intake of the 400ml (300kcal) Nottingham Test Meal is tolerated by all healthy controls and >95% of patients with functional dyspepsia without inducing vomiting.
Objectives:	The aim of the present study is to find out if the regular intake of Amara has effects on the perceived symptom burden reported by patients with functional dyspepsia. Since dyspeptic symptoms may be associated with abnormal gastric motor and sensory function, these aspects will be assessed by validated methods.

Outcomes:	Primary objective / outcome measure: • change in perceived symptom burden during regular intake of Amara assessed by the Leuven Dyspepsia Score between visit 1 (off treatment) and 3 (on treatment). Secondary objectives / outcome measures • Assess effect of Amara on other gastrointestinal symptoms using validated, patient related outcome measurements (reflux disease questionnaire, IBS Symptom Severity Score) • Assess effect of Amara on (i) visceral sensitivity and (ii) gastric emptying (^{13}C-breath test) in patients with functional dyspepsia with validated 400ml Liquid Nottingham Test Meal. • Assess effect of Amara on pre- and post-prandial gastric electrical activity (Gastric Alimetry System) and heart rate in patients with functional dyspepsia with validated 400ml Liquid Nottingham Test Meal
Study design:	Prospective, open, monocentric, single arm study (phase IV) as Investigator-Initiated Trial (IIT)
Inclusion / Exclusion criteria:	Inclusion criteria: • Patients referred by their treating physician to the Center for integrative Gastroenterology at the Clinic Arlesheim • Age over 18 years and ≦75 years of age • Patients with Diagnosis of Functional Dyspepsia with Postprandial Distress (Rome IV criteria) with Leuven Dyspepsia Score “at least moderate” severity (≥2/4) on at least two subscales (≥4 total) • Signed informed consent • No change in medical treatment (e.g., proton pump inhibitor, antidepressants) during the last one month or for the duration of the period • Good German or English knowledge (at least level B2 from Common European Framework of Reference for Languages) Exclusion criteria: • Acute life-threatening conditions • Withdrawal of informed consent • Clinically relevant psychiatric comorbidity (HADS score ≥14) • Advanced liver (Child score > 6) or kidney disease (GFR < 60) • History of major gastrointestinal surgery (appendectomy, hysterectomy, cholecystectomy, hernia repair are not exclusion criteria) • Allergy to any component of Amara • Pregnancy and lactation
Measurements and procedures:	Participants will fill in a series of questionnaires two times.

Study Product / Intervention:	In this study the test medication (Amara drops) will be taken by the participants before meals. The herbal preparation is manufactured by Weleda AG, Arlesheim. Besides the bitter substances Artemisia absinthium, Cichorium intybus, Juniperus and Gentiana lutea, Amara Drops contain also Centaurium, Peucedanum, Achillea millefolia, Salvia officinalis and Taraxacum, all suspended in an alcohol-based tincture. The full indication text licensed by Swissmedic is: “According to the anthroposophical knowledge of man and nature, Weleda Amara-Drops can be used for digestive complaints such as heartburn, flatulence and bloating after meals, to stimulate the bile flow and for loss of appetite and nausea. The effect of Weleda Amara drops is based on a balanced mixture of medicinal plants with tonic (invigorating) and aromatic bitter substances, which are suitable for stimulating digestion. Weleda Amara drops mildly stimulate the secretion of saliva and gastric juices, promote the formation and secretion of bile and thus facilitate the digestion of fats. In addition, they are effective against flatulence and cramps.”
Control Intervention:	No control group
Number of Participants with Rationale:	Participants: 60 patients with functional dyspepsia with postprandial distress (Rome IV criteria). There are no previous studies that have assessed the effect of Amara Drops in functional dyspepsia. Before randomized double blind controlled studies can be considered it is appropriate to assess perceived changes in symptom burden and physiological effects of Amara in clinical practice. At the same time the feasibility of recruiting this patient group and performing gastric emptying and other studies will be assessed. In this prospective open label study, placebo effects are likely to be present. Previous randomized controlled trials indicate that this can be up to 40%. To demonstrate convincing evidence of clinical efficacy a minimum 60% response rate above no treatment (run-in phase) must be demonstrated. Based on these considerations, for the primary outcome, power calculation suggests that at least 58 patients are required to detect moderate effects on perceived symptom burden at a convincing level of statistical significance (beta 0.9, alpha <0.01).
Study Duration:	2 years
Study Schedule:	Month Year of First-Participant-In (planned): July 2022 Month Year of Last-Participant-In (planned): August 2024 Month Year of Last-Participant-Out (planned): September 2024
Investigator:	Prof. Dr. med. Mark Fox Leitender Arzt, Zentrum für Integrative Gastroenterologie Leiter, Magen Darm Funktion: Basel, Labor und Klinik für funktionelle Magendarm Erkrankungen und Motilitätsstörungen Tel. +41 (0)763580379 mark.fox@klinik-arlesheim.ch
Study Centre:	Single Centre, Clinic Arlesheim (CLA), Pfeffingerhof 1, 4144 Arlesheim

Statistical Considerations:	Differences between the scores from the primary and secondary outcome measurement variables – at baseline (following run-in) and after either 4-weeks treatment - will be compared initially by t-test if the data is normally distributed and Wilcoxon rank sum test when data are not normally distributed. In addition, we will perform univariate and multivariate linear regression analysis in which potential covariates will be considered; confounding will be evaluated by adding these variables to the linear regression model and looking at the change of the regression coefficients. These variables will include participants' gender, age, perceived symptom severity and gastric function at baseline. In the analysis of the primary outcome two-tailed p ≤0.05 will be considered statistically significant. Since the evaluation of the secondary endpoints is purely exploratory, other p-values will be calculated but reported without claiming significance,
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

ABBREVIATIONS

13C BT	^{13}C Acetate Breath Test
AE	Adverse Event
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV)*
CRF	Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
eCRF	Electronic Case Report Form
EKNZ	Ethikkommission Nordwest- und Zentralschweiz
HADS	Hospital Anxiety and Depression Scale
GCP	Good Clinical Practice
HRA	Federal Act on Research involving Human Beings *(in German: HFG)*
HRV	Heart Rate Variability
IB	Investigator's Brochure
IBS-SSS	Irritable Bowel Syndome Symptom Severity Score
ICS	Internal Coherence Scale
IIT	Investigator-initiated Trial
KLA	Klinik Arlesheim
LCT	Lüscher Colour Test
LDQ	Leuven Dyspepsia Questionnaire
NTM	Nottingham Test Meal
OTC	Over The Counter
PHQ-12	Patient Health Questionnaire 12-items, depression module
PI	Principal Investigator
RCT	Randomised Controlled Trial
RDQ	Reflux Disease Questionnaire
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

STUDY SCHEDULE

Study Periods	Screening	Physiological Measurement and Treatment	Physiological Measurement and End
Visit	1	2	3
Time (days)	Ca. -14-28d	1	28±14d
Medical History and Demographics	x		
Leuven Dyspepsia Questionnaire (LDQ)	x		x
Screening questionnaires	x		
Pregnancy test (urine)	x	(x)	
In-/Exclusion Criteria	x		
Patient Information and Informed Consent	x		
Primary Outcome Measure: LDQ total score	x		x
Secondary Outcome Measure: other GI symptom questionnaires	x	x	x
Lüscher Colour Test	x	x	x
Physiological Measurement (13C BT, HRV)		x	x
Intake of the Study Medication (Amara Drops)		x	x
Compliance with therapy			x
Satisfaction with therapy / Whether a prescription of Amara is wanted			x
Concomitant Medication, Therapy	x	x	x
Serious Adverse Events	x	x	x

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Prof. Dr med Mark Fox in the position as the Sponsor-Investigator takes on the responsibility as a clinical study sponsor and also conducts the clinical trial.

Prof. Dr. med. Mark Fox

Leitender Arzt, Zentrum für Integrative Gastroenterologie

Leiter, Magen Darm Funktion: Basel, Labor und Klinik für funktionelle Magendarm Erkrankungen und Motilitätsstörungen

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1.2 Principal Investigator(s)

Prof. Dr. med. Mark Fox

Leitender Arzt, Zentrum für Integrative Gastroenterologie

Leiter, Magen Darm Funktion: Basel, Labor und Klinik für funktionelle Magendarm Erkrankungen und Motilitätsstörungen

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1.3 Statistician ("Biostatistician")

Prof. Dr. med. Mark Fox

Leitender Arzt, Zentrum für Integrative Gastroenterologie

Leiter, Magen Darm Funktion: Basel, Labor und Klinik für funktionelle Magendarm Erkrankungen und Motilitätsstörungen

Klinik Arlesheim, CH-4144 Arlesheim

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Mark.fox@klinik-arlesheim.ch

1.4 Laboratory

No laboratory is involved in the trial.

1.5 Monitoring institution

The test centre has commissioned an independent monitor for the implementation of the monitoring visits. The tasked Mrs Susanne Forst holds a Certificate of Advanced Studies (USZ) in Clinical Trial Management. Details are set out in the contract between the two parties.

Susanne Forst, Aufwiesenstrasse 20, 8305 Dietlikon, suforst@googlemail.com, +41 (0)76 794 75 30

1.6 Data Safety Monitoring Committee

Patients in this study are treated for a relatively short time with a drug already on the market and known to have a very good safety profile. Since there are also no prior data to suggest that the intervention being studied has the potential to harm patients, a DSMC is not needed.

1.7 Any other relevant Committee, Person, Organisation, Institution

Advisory Board:

Philipp Busche (chief physician, center for integrative gastroenterology), Clinic Arlesheim

PD Dr Matthias Kröz (medical and study design expertise), Clinic Arlesheim

Dr med Martin Schnelle (medical and study design expertise), Weleda AG

Luitgard Spitznagel (study design, control of data quality and consistency), Weleda AG

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information and consent form as well as other study-specific documents will be submitted to the constituted Competent Ethics Committee (CEC). The decision of the CEC authority concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from the required authority has been received. Any additional requirements imposed by the authorities shall be implemented. Any amendment to the protocol must as well be approved (if legally required) by these institutions.

2.1 Study registration

The current study will be registered at Clinicaltrials.gov. “Number” and “Date” will be announced as soon as possible. In addition, the current study will be registered on the Swiss National Clinical trial Portal.

2.2 Categorisation of study

The study medication Amara is authorised in Switzerland without indication. The full indication text licensed by Swissmedic is: “According to the anthroposophical knowledge of man and nature, Weleda Amara-Drops can be used for digestive complaints such as heartburn, flatulence and bloating after meals, to stimulate the bile flow and for loss of appetite and nausea. The effect of Weleda Amara drops is based on a balanced mixture of medicinal plants with tonic (invigorating) and aromatic bitter substances, which are suitable for stimulating digestion. Weleda Amara drops mildly stimulate the secretion of saliva and gastric juices, promote the formation and secretion of bile and thus facilitate the digestion of fats. In addition, they are effective against flatulence and cramps.” These indications are in accordance with the German Commission C which states the applications of Amara include digestive problems, including dyspepsia. This commission’s role is to advise the Federal Institute for Medicinal Products and Medical Devices on the approval of anthroposophic medicines by providing their anthroposophic medical expertise. Furthermore, in the 15-year period 01.01.3006 - 31.12.2021 only 26 individual case safety reports (ICSR) with 43 adverse drug reactions (ADRs) were reported (see also section 3.4). All these reasons lead us to the conclusion that this study is only associated with minimal risks and should be classified in category A.

2.3 Competent Ethics Committee (CEC)

The investigator Prof Dr med Mark Fox has submitted the application documents to the CEC “Ethikkommission Nordwest- und Zentralschweiz (EKNZ)” for examination. Changes of the protocol will not be implemented until the EKNZ has reviewed and approved them. This does not apply to measures which must be taken immediately to protect the participants or when the changes involve only logistical or administrative aspects of the trial. Amendments are reported according to chapter 2.10. Premature study end or interruption of the study would be reported within 15 days. The regular end of the study will be reported to the CEC within 90 days, the final study report will be submitted within one year after study end.

2.4 Competent Authorities (CA)

Competent Authorities (CA) approval is not necessary for the study requested.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current

version of the Declaration of Helsinki [20], the guidelines of Good Clinical Practice (GCP) [21] issued by ICH. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

Weleda AG, the company that provides the preparations of Amara used in this study supported part of the costs. Weleda AG has had no influence on the design and implementation of the study nor on collection, management or analysis of the data.

2.7 Patient Information and Informed Consent

The consent form will be submitted when the patient visits the clinic for the physician-patient consultation. This consultation takes place regardless of whether the patient participates in the study or not. One of the recruiting physicians will then explain to each participant the nature of the study, its purpose, the procedures involved, the rights and obligations, the expected duration, the potential risks and benefits, possible alternatives to the intervention under investigation, and any discomfort it may entail.

Each participant will be informed that the participation in the study is voluntary and that she/he may withdraw from the study at any time and that withdrawal of consent will not affect her/his subsequent medical assistance and treatment and that they will also have the right to be informed at any time of any further questions relating to the clinical trial. All participants will be informed that her/his medical records may be examined by authorised individuals other than their treating physician.

Enough time will be given to the participants to ask questions and to decide whether to participate or not. The participant will read and consider the statement before signing and dating the informed consent form. The consent form will also be signed and dated by the physician. The original will be retained as part of the study records and a copy of the document will be given to the patient. The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure. The study nurse will also attend the interview where the physician informs about the study and is available for additional questions.

Participants will not receive any compensation for participating in this clinical trial.

2.8 Participant privacy and confidentiality

The following aspects are mentioned in the patient consent form and are therefore known to the participants:

The investigator affirms and upholds the principle of the participant's right to privacy and that they will comply with applicable privacy laws. Especially, anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Yet, as written in paragraph 13., if journals wish to have the raw data submitted, we will do so, though data protection will be maintained so that the data cannot be traced back to individuals. Subject confidentiality will be further ensured by utilising subject identification codes to correspond to treatment data in the computer files. For data verification purposes, authorised representatives of the Sponsor, a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, as follows:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise

2.10 Protocol amendments

All study staff are allowed to provide suggestions for a protocol amendment. But the PI is the only one

who is allowed to amend the protocol. Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the CEC. Such deviations will be documented and reported to the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Functional dyspepsia (FD) with postprandial distress is a common functional gastrointestinal (GI) disorder characterized by the occurrence of epigastric symptoms such as early satiety (fullness), nausea and upper abdominal pain after meals at least twice a week over at least six months (Rome IV criteria).(1) By definition, no structural disease is found on routine laboratory, endoscopy or imaging studies. Instead, symptoms are thought to be related to abnormal gastrointestinal motility (e.g. impaired gastric relaxation, abnormal emptying) and increased sensitivity to gastric distension and the digestive process.(2) Additionally, detailed studies of the mucosa often reveal low-grade inflammation in the duodenum and hyperpermeability ("leaky gut").(3)

Epidemiological studies report a 10-30% prevalence of functional dyspepsia (FD).(4) When dyspeptic symptoms are short in duration and relatively mild, many patients wish to self-manage with dietary adaptation and /or over the counter (OTC) preparations.(5) Others report high rates of intolerance to prescription medications.(5, 6) In these patients complementary and alternative medicines (CAM) based on natural products, such as plant-based "phytotherapy", are particularly appealing.(7) Several herbal therapies for functional dyspepsia have been tested in randomized clinical studies.(8) These include phytochemicals such as peppermint oil that inhibits smooth muscle contraction by direct blockade of calcium channels and other effects, deglycyrrhizinated licorice that increases gastric mucus secretion and may enhance mucosal protection and other preparations that combine multiple herbal products with the intention of inducing synergistic effects that promote normal digestive function.(9) In particular, STW-5 (Iberogast©, Bayer) has been shown to have physiological effects on gastric accommodation and contractility. A double-blind non-inferiority randomized control trial (RCT) comparing Iberogast to cisapride (5-HT4 agonist) showed equal effectiveness for both medications,(10) and a meta-analysis of 3 double blind RCTs provided evidence that Iberogast is more effective than placebo in the treatment of dyspeptic symptoms.(11)

Amara Drops (Weleda, Arlesheim, Switzerland) is a proprietary preparation used for many decades in anthroposophic medicine that is marketed for the treatment of functional digestive disorders. Patients take 10-20 drops before meals to relieve loss of appetite, bloating, nausea, and other dyspeptic symptoms. These bitter substances are thought to promote digestion and relieve symptoms by stimulating the secretion of gastric and pancreatic enzymes, upper gastrointestinal motility and gastric emptying. These prokinetic effects may be therapeutic in patients with functional dyspepsia because there is an association between delayed gastric emptying (GE) and upper gastrointestinal symptoms including uncomfortable fullness, nausea and vomiting.(2, 12, 13) To date, the effects of Amara has not been subjected to pre-clinical or clinical studies.

The primary aim of this investigator-initiated, prospective, open-label, therapeutic study is to test if Amara has effects on the perceived severity of abdominal symptoms in patients with functional dyspepsia. Additionally, the physiological effects of Amara on gastric motor and sensory function will be assessed using validated methods

To test this, a prospective, open label, non-randomized study will assess (i) Perceived effects of regular intake of 10-20 Amara Drops prior to main meals on dyspeptic symptoms using the validated Leuven Dyspepsia Questionnaire. (ii) Physiological effects of 20 drops Amara tincture on gastric emptying using the 400ml Nottingham Test Meal with non-radioactive ^{13}C-acetate breath test and concurrent assessment of filling sensation and dyspeptic symptoms by Visual Analogue Scores (VAS). (iii) In a subset of 20 consecutive patients, gastric electrical activity before, during and after ingestion of the test meal will be measured using the non-invasive Gastric Alimetry System (high-resolution gastric mapping / electro-gastrography) with concurrent heart rate monitoring. Gastric Alimetry is a diagnostic test for patients with chronic gastric symptoms, a development of electrogastrography that maps gastric

neuromuscular activity using a large array of electrodes over the abdomen. The test can help differentiate if patients have gastric neuromuscular dysfunction, gastric sensory disorder, gastric outlet obstruction or a functional (central) cause of symptoms. Individuals that fulfill the diagnostic criteria for functional dyspepsia with postprandial distress syndrome according to the Rome IV criteria will be recruited. At the first study visit (Study visit #1), Symptom questionnaires and other questionnaires to assess general health and psychiatric well-being will be completed at the time of recruitment. To answer the questions, the study participants are sent a one-time link to the questionnaires. Additionally, a Lüscher Color Test (LCT) will be performed. This non-verbal, non-written test has been developed to assess patient's personality and psychiatric state. This could be of interest in patients with disorders of brain-gut interaction that may not admit to the role of central factors in their illness.

Eligible patients will have no clinically relevant medical co-morbidity or previous gastrointestinal surgery and must have had a normal upper gastrointestinal pan-endoscopy in the previous 3 years. If not known, Helicobacter pylori status will be assessed by ^{13}C-stool antigen test (repeat endoscopy not required). The first visit is followed by a 2–4-week run-in period. The presence and severity of dyspeptic symptoms will be reported using an on-line application downloaded on the patient's smart phone (an electronic reminder will be sent at 21:00 every day).

The LCT will be repeated during the second study visit (Study visit #2). At this time, gastric function will be assessed by ^{13}C-breath test measurements with concurrent assessment of visceral sensitivity.

Amara Drops will be dispensed with 10-20 drops (0.25-0.50ml) taken three times a day before meals for 4 weeks. The patients are free to vary the dose within these parameters as considered appropriate. The amount taken will be monitored by checking the volume remaining in the bottle at the end of the 4-week intervention. During this time, patients will continue entering their symptoms and any side effects into the app.

At the end of the study period (Study Visit #3) the questionnaires, the LCT and the ^{13}C-breath test measurement with concurrent assessment of visceral sensitivity will be repeated. An e-mail with the questionnaire link will be send to the patient shortly before the third study visit. Additionally, the patients will be asked if their global satisfaction was better on Amara treatment, whether they wish to continue treatment and /or recommend the treatment to others with similar symptoms.

3.2 Investigational Product (treatment) and Indication

Composition of the investigational medicinal product (IMP): The herbal preparation is manufactured by Weleda AG, Arlesheim. Besides the bitter substances Artemisia absinthium, Cichorium intybus, Juniperus and Gentiana lutea, Amara Drops contain also Centaurium, Peucedanum, Achillea millefolia, Salvia officinalis and Taraxacum, all nine plant substances held in an alcohol-based tincture.

The full indication text licensed by Swissmedic is: "According to the anthroposophical knowledge of man and nature, Weleda Amara-Drops can be used for digestive complaints such as heartburn, flatulence and bloating after meals, to stimulate the bile flow and for loss of appetite and nausea. The effect of Weleda Amara drops is based on a balanced mixture of medicinal plants with tonic (invigorating) and aromatic bitter substances, which are suitable for stimulating digestion. Weleda Amara drops mildly stimulate the secretion of saliva and gastric juices, promote the formation and secretion of bile and thus facilitate the digestion of fats. In addition, they are effective against flatulence and cramps."

3.3 Preclinical Evidence

Results from preclinical investigations for the individual plant-based preparations in Amara indicate a very good safety profile (personal communication Prof. Dr. Carsten Gründemann, Departement Pharmazeutische Wissenschaften, Translationale Komplementärmedizin, Universität Basel). This supports the clinical experience that Amara is very unlikely to cause ADRs in patients.

3.4 Clinical Evidence to Date

Prospective studies on the treatment of dyspepsia have been performed with a variety of aromatic bitter substances and suggest very good safety/tolerability. Meta-analysis of studies also confirmed that these plant-based products can be effective in the management of functional dyspepsia.(8, 11)

It has also been observed that Anthroposophic physicians which participated in the Evaluation of anthroposophic medicine (EvaMed) network in Germany very often prescribed Amara drops for dyspeptic symptoms.(14) Based on the observations of the lead investigator, gastroenterology colleagues and the EvaMed data, significant improvements in dyspeptic symptoms often reported.

Based on information provided by the manufacturer, in the 15-year period 01.01.3006 - 31.12.2021 only 26 individual case safety reports (ICSR) with 43 ADRs were reported. 3 non-serious ICSR occurred in Switzerland; 1 serious and 22 non-serious ICSR occurred in Germany. Most ADRs occurred within the System Organ Classes (SOC) skin and subcutaneous tissue disorders (11) and gastrointestinal disorders (9). One ICSR was assessed as serious due to hospitalisation. The reported ADR was acute liver failure and acute renal failure after user of Amara Drops (for about 15-22 days) and Paracetamol (duration and dosage unknown). As none of the active ingredients of Amara Drops are known to be hepatotoxic, the causal relationship was assessed as unlikely for Amara Drops. But for Paracetamol the causal relationship was assessed as possible due to the known hepatotoxic potential.

3.5 Dose Rationale

Patients will take 3 x 10-20 drops of Amara before meals daily for four weeks (see section 8.1). The standard dose of this preparation is 10-15 drops before meals to “stimulate the digestive process”; however, patients are encouraged to adapt the dose to their requirements. Patient compliance will be assessed using a smart phone application that will record whether medication was taken and the severity of symptoms at the end of each day. Patient compliance (i.e. actual intake) will be checked by weighing the bottle at the end of the treatment period.

A 2-4-week run-in period between screening and the start of treatment is applied to ensure that the severity of symptoms is representative (patients tend to present during periods with relatively severe symptoms, thus run-in periods reduce the influence of spontaneous “regression to the mean” providing false positive results). The treatment period of 4-weeks is in accordance with the above-mentioned studies for other aromatic bitter substances and represents the minimum recommendation for study duration in functional gastrointestinal disorders.(15)

3.6 Explanation for choice of comparator (or placebo)

No comparator will be used in this study.

3.7 Risks / Benefits

The initial assessment of patients with functional dyspepsia will adhere to international guidelines on the investigation of this condition. It is widely recognized that current pharmacological treatment for dyspepsia is sub-optimal and new options are to be welcomed.

Amara Drops (Weleda) is a proprietary preparation that has been marketed over the counter (OTC) for many years. No serious side effects have been reported. Health status can improve thanks to the treatment used in this study, fewer dyspeptic symptoms could be possible and by participating in the trial, the results can also benefit future patients. However, we cannot guarantee that there will be a benefit from participating in this trial.

There are no expected risks associated with participating in this study. Very rarely, hypersensitivity or intolerance reactions may occur, this could include skin rash or gastrointestinal symptoms. Weleda AG analysed the safety profile of Amara. A pharmacovigilance monitoring between 2006 and 2021 showed very few reports of adverse drug reactions (see section 3.5).

Gastric emptying studies are recommended in patients with functional dyspepsia that do not respond to first-line, dietary management and empirical treatment.(16) Unlike standard investigation of gastric emptying by scintigraphy, the ^{13}C-breath test is not radioactive and is suitable for repeated measurements.(17) The 400ml (300kcal) Nottingham Test Meal is based on a proprietary liquid nutrient drink (Fresubin, Energy Drink) often provided to patients with gastrointestinal and other diseases that require supplementary enteral nutrition. It is not associated with adverse outcomes. Clinical validation studies report that intake of the 400ml NTM is tolerated by all healthy controls and >95% of patients with functional dyspepsia without inducing vomiting.(18, 19)

3.8 Justification of choice of study population

Study participants will be recruited from patients referred to Gastroenterologists at Clinic Arlesheim for

assessment of dyspeptic symptoms. Investigations in this patient group identify an organic cause of these persistent symptoms in less than 1 in 4 cases.(16) Instead, functional dyspepsia is considered to be a disorder of brain-gut interaction, with symptoms related to both abnormal gastric motor function (e.g. delayed gastric emptying) and sensory function (peripheral hypersensitivity but also abnormal central processing).(1) Conservative measures (e.g. reduction in dietary fat) and medical treatment (e.g. acid suppression, prokinetics) often fail to improve symptoms.(5) Moreover, concerns about long-term side effects for certain medications (e.g. domperidone, metoclopramide),(20) and high rates of intolerance to prescription medications are reported.(5, 9) For these reasons, there is a clinical need for new and effective treatments of functional dyspepsia. Complementary and alternative medicines (CAM) based on natural products, such as plant-based “phytotherapy”, are particularly appealing.(7, 9)

There are no previous studies that have assessed the effect of Amara Drops in functional dyspepsia. Before randomized double blind controlled studies can be considered prospective, open-label therapeutic study to assess perceived changes in symptom burden will be performed (at the same time the feasibility of recruiting this patient group and performing gastric emptying and other studies will be assessed). In this prospective open label study, placebo effects are likely to be present. Previous randomized controlled trials of therapy in functional gastrointestinal disorders indicate that this can be up to 40% in this group.(15) To compensate for this confounding factor and to demonstrate convincing changes in perceived symptom burden at least 60% of patients should show improvement on-treatment compared to off-treatment (run-in phase). Assuming a moderate effect (Cohen's effect size of 0.4) on the primary outcome measure (effect size and standard deviation as in a previous paper by Carbone et al. (21)) power calculation suggests that 58 patients are required to detect a significant effect at a convincing level of statistical significance (beta 0.9, alpha <0.01).

Any patients unwilling to participate in the study will not be included the study and will receive appropriate investigation and management that may include ^{13}C breath test assessment of gastric emptying and Amara drops.

Furthermore, we guarantee that a physician not participating in the study, safeguards participant interest and insures proper medical care (P. Busche, Medical Director Internal Medicine, Specialist in Internal Medicine and Gastroenterology at Clinic Arlesheim).

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of the present study is to evaluate whether the herbal drug Amara improves the subjective, perceived burden of abdominal symptoms in patients with functional dyspepsia. It will also assess if the treatment is well tolerated. The present study will also investigate psychological and physiological function. This additional information should provide insight into which patients benefit the most from the treatment with Amara. The results of this prospective, open-label therapeutic study will also inform the study design for any subsequent RCT study in functional dyspepsia.

4.2 Primary Objective

Document perceived changes in upper gastrointestinal, dyspeptic symptoms reported by patients with functional dyspepsia treated with Amara for 4 weeks, as assessed by the Leuven Dyspepsia Score between visit 1 (off treatment) and 3 (after treatment)..

4.3 Secondary Objectives

Assess perceived effect of Amara on other gastrointestinal symptoms using validated, patient related outcome measurements (reflux disease questionnaire, IBS Symptom Severity Score).

Assess effect of Amara on (i) visceral sensitivity and (ii) gastric emptying (^{13}C-breath test) in patients with functional dyspepsia with validated 400ml Liquid Nottingham Test Meal. Repeat testing will also allow an assessment of reproducibility to be obtained (iii) In a subset of 20 consecutive patients, gastric electrical activity will be measured using the non-invasive Gastric Alimetry System (high-resolution gastric mapping / electro-gastrography) with concurrent heart rate monitoring.

Participants will be asked also to rate their overall satisfaction with Amara and the number that request an additional prescription of Amara for the period after the study will be documented, as an indication of

perceived effectiveness.

Additionally, factors that predict the outcome of Amara treatment in functional dyspepsia will be assessed. These factors will include (i) age (ii) sex (iii) severity of dyspeptic symptoms (iv) presence of other gastrointestinal symptoms (v) presence of psychological comorbidity (vi) presence of heightened visceral sensitivity after ingestion of the NTM (vii) abnormal gastric emptying during ^{13}C gastric emptying test (viii) compliance with study procedures.

Additionally, the Lüscher Colour Test will be acquired. This non-verbal, non-written test was developed to provide insights into personality and psychological state. This could be of interest in patients with disorders of brain-gut interaction that may not admit to the role of central factors in their illness. Reproducibility of LCT will be documented by repeating the test at Study visit #1 and #2. Correlation with dyspeptic symptoms, psychological or physiological state will be assessed.

4.4 Safety Objectives

Perceived safety and tolerability will be assessed. For this purpose, participants will be instructed to report possible adverse drug events (ADRs)/ side effects during the treatment period. Participants will be encouraged also to report possible late-onset ADRs that occur after treatment.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome will be the perceived change of dyspeptic symptoms assessed by the Leuven Dyspepsia Questionnaire (LDQ) between visit 1 (off treatment) and 3 (after treatment). The questionnaire contains 3 domains/questions which related to: a) The inability to finish a meal due to early satiety b) The feeling of food lying heavily in the stomach c) Feeling bloated in the stomach. The questionnaire is presented to the patients in the form of three questions which define five grades of severity (0-4), and which are supported by pictograms expressing the associated severity. Higher total scores indicate more severe dyspeptic symptoms. For each subscale 0 normal, 1 mild dyspepsia; 2, moderate dyspepsia; 3, severe dyspepsia; 4, very severe dyspepsia. The questionnaire is to be evaluated on a daily basis and the mean of the values of the three symptoms is proposed to represent the severity of that day. A weekly score can be calculated from the daily scores and is currently proposed for the primary use of the scale.(21)

The LDQ has been developed using standard methods, including focus group interviews and cognitive debriefing interviews.(21) The further validation of the score was undertaken with the means of interventional studies, evaluating the response of this questionnaire to prokinetic and neuromodulatory medications. The LDQ has shown to be a good rating scale to be used as a severity indicator of dyspepsia and can be given to the same patient in subsequent sessions to track the change in symptoms. A minimally clinically important difference has also been determined. The results of this validation work have been published in peer reviewed journals.(22, 23)

The Leuven Postprandial Distress Scale, which is supported by the European Medicines Agency, is a sensitive and reliable patient-reported outcome instrument to assess symptoms in the functional dyspepsia/postprandial distress syndrome. Based on this information, the LDQ variable will be the main result to verify whether the test medication in this trial is efficacious. In this open-label study in which placebo and treatment effects are summed we expect a moderate to large >60% reduction in mean symptom burden as measured by the LDQ (results will be shown as mean ± SD).

5.2 Secondary Outcomes

Secondary objectives / outcome measures

- Assess perceived effect of Amara on other gastrointestinal symptoms using validated, patient related outcome measurements (reflux disease questionnaire, IBS Symptom Severity Score)
- Assess effect of Amara on (i) visceral sensitivity and (ii) gastric emptying (^{13}C-breath test) in patients with functional dyspepsia with validated 400ml Liquid Nottingham Test Meal. Details of the acquisition and analysis of these physiological measurements are in the appendix (SOP). (iii) gastric electrical activity before, during and after the test meal as assessed by the Gastric Alimetry System (concurrent measurements of heart rate will also be acquired)

- Overall satisfaction with Amara treatment will be assessed by a 100mm visual analogue scale and whether ongoing prescription is wanted (yes/no).

5.3 Other Outcomes of Interest

The validity of the Lüscher Colour Test (LCT) in the assessment of patients with functional dyspepsia will also be assessed. This will include face validity (debriefing session), construct validity (comparison with validated questionnaires assessing psychological patient related outcome measures), reproducibility (test re-test validity before and after run-in period), and internal consistency. Sensitivity of LCT to any change in dyspeptic symptoms, psychological or physiological state that occurs during the treatment study will also be documented.

5.4 Safety Outcomes

All perceived events and side effects will be entered by the participant when filling in the questionnaire. In addition, they will report any SAE to the study team by use of the mobile application or telephone (even after study end/discontinuation until the adverse effect subsides).

Previous placebo-controlled trials that studied the effects of another aromatic bitter preparation in patients with dyspepsia reported side effects similar to placebo.(11) Additionally, safety monitoring has identified very few ADRs in the last 15 years (see section 3.4). Participants can indicate possible side effects in the questionnaire booklet. Furthermore, participants are instructed to report the start and duration, the severity (minor, moderate, severe) of the side effect and what have been done about it.

6. STUDY DESIGN

6.1 General study design and justification of design

The present IIT (Investigator-Initiated Trial) study is a prospective, open, monocentric, single arm, intervention study (phase IV) of the category A, as defined in the Ordinance on Clinical Trials in Human Research (ClinO) of 20 September 2013 (D. S. Bundesrat, “Verordnung über klinische Versuche in der Humanforschung,” vol. 2013, no. September, pp. 3407–3454, 2013), on the basis of the Human Research Act (HRA) of 30 September 2011 (Die Bundesversammlung der Schweizerischen Eidgenossenschaft, “Bundesgesetz über die Forschung am Menschen (Humanforschungsgesetz, HFG),” vol. 1313, no. September, pp. 1–26, 2011).

A past survey showed that among Anthroposophical physicians the most frequent diagnosis group where Amara preparations are prescribed are gastrointestinal disorders such as dyspepsia and irritable bowel syndrome (Eva-Med Network 2009, data on file); however, prospective clinical studies have not been performed. In the present study we therefore want to investigate the effectiveness of Amara drops in patients with functional dyspepsia diagnosed according to Rome IV criteria.(1)

Study participants will be recruited among the patients referred to the Department of Integrative Gastroenterology at the Clinic Arlesheim. Recruitment period will last 18 months. This duration is very cautiously estimated with basis on expected at least two referrals for assessment of dyspeptic symptoms per week. Best clinical care will be provided regardless of whether the patient is eligible and / or consents to participate in the study.

At the initial screening assessment at Clinic Arlesheim, patients will be informed about the study by one of the research team. If the participants fulfil the inclusion criteria and consent to participate, then the team member will administer the questionnaires and help the participant download the mobile application to monitor symptoms onto their smart phone (paper version available). Participants who signed the informed consent form will fill in a questionnaire with questions about dyspeptic (LDQ) and other gastrointestinal symptoms (RDQ, IBS-SSS), anxiety and depression (HADS), somatization (PHQ15), the Internal Coherence Scale (ICS) and the Lüscher Colour Test (LCT).

An appointment will be made 2-4-weeks later for the second study visit at which time the ^{13}C gastric emptying study will be performed again. The run-in period is 2-4-weeks. This reduces the influence of spontaneous “regression to the mean” (i.e., false positive results).(15)

Gastric motor and sensory function will be assessed by ingestion of the 400ml, 300kcal Nottingham Test Meal (NTM) labelled with ^{13}C acetate. This provides both an assessment of patient symptoms / visceral sensitivity to gastric filling with the 400ml liquid nutrient meal and also an assessment of gastric emptying. The 400ml NTM can be ingested by >95% of patients with functional dyspepsia.(19,

24) The ^{13}C isotope is not radioactive, it takes 2-hours to complete and this technique is very appropriate for repeated assessment of gastric emptying.(16) In a subset of 20 consecutive patients, gastric electrical activity will be measured before, during and after ingestion of the Nottingham Test Meal using the non-invasive Gastric Alimetry System (high-resolution gastric mapping / electro-gastrography). Concurrent heart rate monitoring will provide an assessment of cardiovagal tone / autonomic nervous function.

The treatment period with Amara drops is four weeks per patient; participants will be instructed to take 10-20 drops of the herbal medicine Amara three times a day before meals over 28 days. This treatment period is in accordance with previous studies for aromatic bitter substances and represents the minimum recommendation for study duration in functional gastrointestinal disorders.(15) During the treatment period patients will record their symptoms using a mobile application (reminder will be sent at 21:00 every day). In addition, patients can note side effects that they perceive to be caused by Amara. If participants do not regularly provide this information, then a team member will call to ask if they have any problems.

At the end of the treatment period the participant will return to Clinic Arlesheim for repeat assessment. The LDQ and other patient related outcomes will be assessed again and ^{13}C gastric emptying study will be repeated on treatment.

At the end of the study, all participants will return the supply of Amara. The study team will assess compliance by counting the empty bottles and weighing partly used bottles. Patients will be asked whether they wish to continue the medication (yes / no). If the response is positive, then ongoing treatment will be recommended. Amara is classified by Swissmedic as dispensing category D available following discussion with specialist without prescription („Abgabekategorie D: «Abgabe nach Fachgespräch»).

Overall, approximately 30 minutes will be needed to complete the questionnaires on each occasion. The total time required per patient during the study is a maximum of 8 hours (reading documents, filling in questionnaires, gastric emptying study (twice)).

During the period the participants are enrolled in this study no additional outpatient examinations are planned. If, while someone is participating in the study, acute symptom occur and the need arises for early outpatient assessment or inpatient admission to the clinic, the study would be terminated for this subject as of this date.

Limitations:

- The study will provide a prospective assessment of perceived treatment effectiveness; however, a large non-specific (placebo) effect is likely to be present as in any open-label, single-arm study in patients with functional gastrointestinal disease. This limitation is factored into the power calculation which requires at least a moderate treatment effect for Amara to be considered effective. Note that the secondary analysis that will identify baseline factors (e.g., age, sex, symptom severity, gastric emptying rate) that associate with treatment effect will be relatively less sensitive to this confounding factor.
- In addition to subjective patient related outcome measures, repeat ^{13}C breath testing with the Nottingham Test Meal on and off treatment will provide physiological assessment of effects of Amara on gastric motor and sensory function. Continuous assessment of patient sensations during Drink tests (i.e., gastric filling) may be less impacted by patient recall than questionnaires. ^{13}C breath testing provides an indirect assessment gastric emptying based on the excretion of $^{13}CO_2$ in the expired air. Although well validated against scintigraphy, it remains uncertain to what extent these results can be affected by individual patient factors other than gastric emptying (e.g. metabolism). Note that this limitation will not affect the results of this study because we will compare gastric emptying in patients on and off Amara treatment (i.e., patients act as their own control).
- Amara drops will be distributed for self-administration at home, thus, we rely on participants to report their intake accurately. Compliance will be checked as described above.
- The four-week duration of drug intake is relatively brief and may underestimate the treatment effect.
- This study may suffer from the limitation that participants will take other over the counter medications or engage in other treatments at home.
- This study design does not allow evaluating the efficacy of Amara medication. However, the aim of this prospective study is to acquire results on overall effectiveness that will inform the design of a randomized controlled study with this aim.

6.2 Methods of minimising bias

6.2.1 Randomisation

Not applicable.

6.2.2 Blinding procedures

Not applicable.

6.2.3 Other methods of minimising bias

- Validated questionnaires will be used, and a statistical analysis plan is included in the protocol.
- Participants will record symptoms daily using a mobile application (paper version available). The study nurse will call participants if this technology is not used regularly.
- Objective assessment of gastric motor and sensory function will complement patient related outcome measurements.
- Compliance will be checked at the end of the treatment period.

6.3 Unblinding Procedures

Not applicable.

7. STUDY POPULATION

Patients with dyspeptic symptoms referred to gastroenterologists at Clinic Arlesheim for specialist investigation and management will be screened for eligibility.

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Patients referred by their treating physician to the Center for integrative Gastroenterology at the Clinic Arlesheim
- Age over 18 years and ≦75 years of age
- Patients with diagnostic criteria of Functional Dyspepsia with Postprandial Distress (Rome IV criteria) with Leuven Dyspepsia Score “at least moderate” severity (≥2/4) on at least two subscales (≥4 total). Normal endoscopy in previous 3 years.
- Signed informed consent
- No change in medical treatment (e.g., proton pump inhibitor, antidepressants) during the last one month or for the duration of the period
- No planned introduction or dose increases of (conventional) anxiolytics or antidepressants during the last one month or for the duration of the period
- Good German knowledge (at least level B2 from Common European Framework of Reference for Languages)

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Acute life-threatening conditions
- Withdrawal of informed consent
- Clinically relevant psychiatric comorbidity (HADS score >11 for anxiety or depression)
- Advanced liver (Child score > 6) or kidney disease (GFR < 60)
- History of major gastrointestinal surgery (appendectomy, hysterectomy, cholecystectomy, hernia repair are not exclusion criteria)
- Allergy to any component of Amara
- Treatment with Amara during the last one month prior to the study
- Pregnancy and lactation

7.2 Recruitment and screening

Patients referred for investigation of dyspeptic symptoms will be called by the department secretary or

a member of the team to make an appointment for their initial screening consultation at the Clinic Arlesheim. As also described in section 6.1, participants will then come to their initial consultation at the Clinic Arlesheim. If after this consultation the recruiting physician considers functional dyspepsia to be the diagnosis according to Rome IV classification, then the LDQ screening instrument will be used to confirm the presence and assess the severity of dyspepsia. A score of “at least moderate” severity (≥2/4) on at least two subscales (≥4 total) is the cut-off for study entry. Patients with clinically relevant, severe anxiety and depression will also be excluded (HADS ≥14). If no recent results are available, blood tests will be obtained to assess liver and kidney function. Total bilirubin, serum albumin, prothrombin time, ascites, hepatic encephalopathy and creatinine levels will be tested. At the screening visit, the LDS and HADS questionnaires will be completed at the time of recruitment and used as screening instruments. This data will be collected using an on-line application (paper versions also available). To rule out pregnancy, women of childbearing potential must take a pregnancy test.

If the patient fulfils all inclusion criteria and none of the exclusion criteria, the patient will be asked if she/he wants to participate. If she/he does want to participate, she/he will sign the informed consent form and will be included in the study. If desired, the study nurse will help the subjects to fill in the demographic details and further questionnaires detailed in the method above.

No payment will be given to study participants. Neither the subjects nor their health insurance companies incur additional costs in connection with participation in this study.

7.3 Assignment to study groups

The present trial is a single arm study.

7.4 Criteria for withdrawal / discontinuation of participants

In emergency situations, where acute symptoms develop or side effects are suspected to be associated with the Amara intake, treatment can be discontinued. The participation can also be terminated by the PI, by the Clinic Arlesheim or by the manufacturer of Amara if there is a suspicion of damage to health caused by the drug or a product defect, respectively. Also, as mentioned before, if there are any signs of patients unwilling to participate in the study it will result in the participant being excluded from the study.

If a participant does no longer fulfil the eligibility criteria at some point of the study, it will lead to the discontinuation of this participant from the study.

Participant recruitment will continue until 60 patients have completed the treatment arm of the study.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment / medical device)

The dosage of Amara is 3 x 10-20 drops per day prior to meals.

8.1.1 Experimental Intervention (treatment / medical device)

The bitter substances Artemisia absinthium, Cichorium intybus, Juniperus and Gentiana lutea, Amara Drops contain also Centaurium, Peucedanum, Achillea millefolia, Salvia officinalis and Taraxacum are held in an alcohol-based tincture. Amara is an herbal preparation manufactured by Weleda AG (Switzerland), according to Good Manufacturing Practice.

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

No control intervention.

8.1.3 Packaging, Labelling and Supply (re-supply)

The Amara drops to be used in this study are a standard commercial product. They will be available in the standard labelled, brown glass. One glass bottle contains 50ml (enough for minimum 100 doses à

20 drops). The manufacturer Weleda AG will supply us with the medication in batches. The pharmacy at Clinic Arlesheim will print instructions on the dose and when to take the medication on an additional label.

8.1.4 Storage Conditions

The recommended storage temperature 15-25° C will be complied with. The Amara bottles to be used in the study will be stored in a lockable medicine cabinet at the out-patient clinic in an air-conditioned room at constant temperature. 60 glass bottles can be stored at once.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

See chapter 8.1.1.

8.2.2 Control Intervention

No control intervention.

8.3 Dose modifications

Participants can vary the dose of the prescribed drug dose within set limits (10-20 drops with meals). This should not be exceeded even in case of worsening symptoms.

8.4 Compliance with study intervention

Compliance will be assessed by a smart phone app (patients will be asked to confirm intake every day). At the end of the study, the bottles will be weighed to determine the actual dose taken during study procedures. Before analysing the data, we will determine the target-actual-difference of the Amara drops taken for each participant. Less than 50 % of prescribed intake is considered as insufficient compliance. In case of insufficient compliance of participants, those data have to be excluded from the per protocol analysis.

8.5 Data Collection and Follow-up for withdrawn participants

In the event of withdrawal, the data collected up to this point will continue to be used.

8.6 Trial specific preventive measures

Treatment with Amara during the last one month prior to the study is not permitted and leads to the exclusion of the study. No specific preventive measures are necessary.

8.7 Concomitant Interventions (treatments)

Current medications, such as acid suppression or antidepressants, can continue to be taken by the participants during the study without dose increase or decrease. This also includes all self-purchased preparations that are available without a doctor's prescription and complementary-medical preparations. Participants will record the use of additional medication in the CRF. They also have to record if they are being treated by other physicians during the study.

8.8 Study Drug Accountability

Immediately after handing out the study drug a receiving inspection will be carried out using the delivery note and the order form. Information on quantities, batch number, damages and shelf life will be recorded in writing in the corresponding Standard Operating Procedure (SOP) document.

In case a participant has signed the informed consent, at the end of the consultation one 50ml bottle of Amara will be given to the participant to take home. The distribution of the test substance will be signed

by the participant and IP on the SOP document. Drugs with the shortest expiry date will be distributed first. Regular expiration date checks will be carried out.

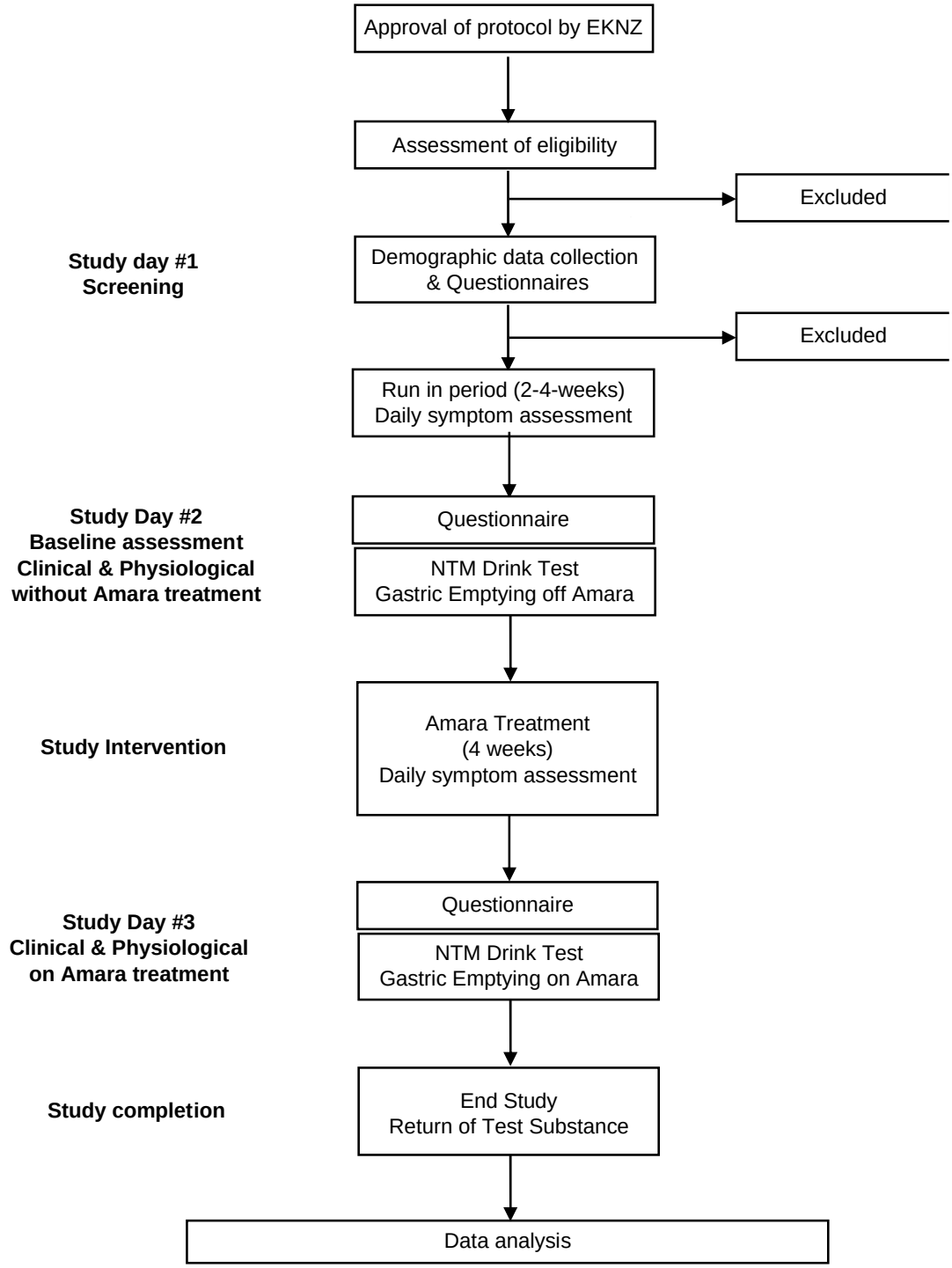
Patient compliance will be assessed using a smart phone application that will record whether medication was taken and the severity of symptoms at the end of each day. Patient compliance (i.e. actual intake) will be checked by weighing the bottle at the end of the treatment period.

8.9 Return or Destruction of Study Drug

Participants are asked to send back the glass with the remaining liquid. The study team will check compliance (i.e. actual intake) by weighing the bottle at the end of the treatment period and then send the investigational product to the pharmacy (Apotheke Klinik Arlesheim) for destruction. The handover will be documented in writing in a SOP.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments



9.2 Assessments of outcomes

The primary study outcome of dyspeptic symptoms will be assessed by the LDQ three times (screening, baseline, study completion).

Secondary study outcomes will be assessed (i) by other validated questionnaires assessing gastrointestinal and psychological comorbidity as well as (ii) by physiological measurement of gastric motor and sensory function using the NTM Drink Test with ^{13}C measurement of gastric emptying (section 5). Additionally, the Lüscher Colour Test will be performed to assess the psychological state and personality profile potentially changing during treatment (section 5.3).

9.2.1 Assessment of primary outcome

See section 5.1.

9.2.2 Assessment of secondary outcomes

See section 5.2.

9.2.3 Assessment of other outcomes of interest

See section 5.3

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

AEs will be recorded, although the Swiss law on clinical research does not require the documentation of AEs for Category A drug trials. Participants will record possible side effects in the app or booklet and are instructed depending on urgency to get in touch with the team of doctors.

Information to be collected about side effects can be seen in chapter 5.4.

9.2.4.2 Laboratory parameters

Urine pregnancy tests will be carried out during the screening visit. In emergency situations laboratory parameters may be assessed if required.

9.2.4.3 Vital signs

No vital signs will be assessed in the context of the study except in emergency situations which may require it.

9.2.5 Assessments in participants who prematurely stop the study

Assessments in participants who are withdrawn from the study prematurely, depend on the type and severity of the SAE. Participants who are withdrawn from the study prematurely due to the occurrence of exclusion criteria other than SAEs will not require any follow-up.

See chapter 10. for further information about follow-ups for participants who prematurely stop the study.

9.3 Procedures at each visit

9.3.1 Screening visit

At the orientation consultation/screening visit the investigator will review the case notes, investigation results (e.g., laboratory tests, gastroscopy) and interview the patient to ensure that inclusion and exclusion criteria are met. In order to comply with the inclusion criteria, pregnancy tests will be performed on all women of childbearing age. At the screening visit, the LDS and HADS questionnaires will be completed at the time of recruitment and used as screening instruments. This data will be collected using an on-line application. After inclusion, further health-related questionnaires will be completed and

the Lüscher Color Test will be performed.

A time is booked 2-4 weeks later for the second study visit. A mobile application will be downloaded onto the personal smart phone device (Symptom Tracker, Gastric Imaging & Analysis GmbH). Paper forms are available if required. During the 2-4 week “run-in” period patients will document their symptoms every day using a mobile application. A reminder will be sent to complete this electronic form every day at 21:00.

9.3.2 Study visits

On the second visit, patients will complete a combined assessment of gastric motor and sensory function off treatment with the Nottingham Test Meal, with gastric emptying documented by ^{13}C-Breath Testing. On completion of the test, the test substance will be provided to the patient with instructions on how and when to take the Amara. An appointment will be made 4-6 weeks after this appointment for the third and final visit. Based on this, the start day for the intervention will also be determined.

During the 4-week intervention, 10-20 drops of Amara will be taken prior to every meal. Patients will document their symptoms every day using a mobile application. Adverse events can also be recorded. Paper forms are available if required. A reminder will be sent to complete this electronic form every day at 21:00.

Shortly before the third study visit participants receive an e-mail with a questionnaire link. All questionnaires will be completed again. If it is noted during the visit that the questionnaires has not been filled in, this can be done in the waiting room or during the visit. The patient will complete a combined assessment of gastric motor and sensory function on Amara treatment with the Nottingham Test Meal, with gastric emptying documented by ^{13}C-Breath Testing. On completion of the test, in addition to the PROM, the patient will be asked about their subjective assessment of the intervention, whether ongoing treatment is desired and whether they would recommend the treatment to other patients with functional dyspepsia. Additionally, compliance with study procedures will be assessed (bottle(s) of Amara will be weighed). At the end of the study, patients are reimbursed a lump sum of 50 Swiss francs for expenses (gas, parking fee, train ticket etc.). More can be provided if an invoice supported by receipts is sent to the principal investigator.

In a subset of 20 consecutive patients, gastric electrical activity will be measured before, during and after ingestion of the Nottingham Test Meal on the second and third study visit using the non-invasive Gastric Alimetry System (high-resolution gastric mapping / electro-gastrography). Concurrent heart rate monitoring will provide an assessment of cardiovagal tone / autonomic nervous function.

10. SAFETY

10.1 Drug studies

The Sponsor’s SOPs provide more detail on safety reporting.

During the entire duration of the study, all unexpected adverse events (UAW) and serious adverse events (SAEs) are collected, investigated, and documented in source documents and case report forms (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An **Adverse Event (AE)** is any untoward medical occurrence in a patient, or a clinical investigation participant administered a pharmaceutical product, and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.3]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,

- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

The Sponsor-investigator makes a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

Grades for severity described in the “Common Terminology Criteria for Adverse Events CTCAE Version 5.0 may be used.

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

As stated in the contract between the Clinic Arlesheim and Weleda AG, we will comply with our pharmacovigilance obligations. UAWs, SAEs and SUSARs will be reported to Weleda AG (see contact below) within a maximum of 24 hours. Any other side effects which are collected through the questionnaires will be notified to Weleda AG as soon as possible.

Address: WELEDA AG, Dychweg 14, CH-4144 Arlesheim

Contact: Yvonne Bäckert, +41 79 793 52 30, pharmacovigilance@weleda.ch

Reporting of SAEs:

All SAEs must be reported immediately and within a maximum of 24 hours to the PI of the study. The PI will re-evaluate the SAE and make a causality assessment of the event to the study drug.

SAEs resulting in death are reported to the Ethics Committee via BASEC within 7 days.

If the possibility arises that a patient can admit the Clinic Arlesheim earlier than expected, it will lead to the discontinuation of this participant from the study. This hospital stay will not be considered as an SAE. Additionally, if a SAE is a clear result of the underlying disease, this SAE is exempted from expedited reporting.

Reporting of SUSARs

The Sponsor-Investigator needs to report SUSARs to the Ethics Committee via BASEC within 7 days, if the event is fatal, or within 15 days (all other events).

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the Ethics Committee via BASEC.

Reporting and Handling of Pregnancies

Pregnant participants will be excluded from the clinical study

Periodic reporting of safety

An annual safety report is submitted once a year to the local Ethics Committee via PI.

10.1.3 Follow up of Serious Adverse Events

In case of participants terminating the study with reported ongoing SAEs beyond alert, participants will have a follow-up check-up as soon as the patient is hospitalized at the Clinic Arlesheim. The procedures depend on the type and severity of the SAE.

11. STATISTICAL METHODS

11.1 Hypothesis

Null hypothesis: There will be no difference in the primary outcome (LDQ score) between baseline and after four weeks of Amara treatment.

Alternative hypothesis: The LDQ score after four weeks treatment is different from the LDQ-score before the treatment.

In the case of statistical significance, the null hypothesis is rejected and the described difference (reduction or increase) is found to be proven according to the alternative hypothesis.

All secondary outcomes are purely exploratory, where effects are looked at and no Null Hypothesis is tested. This study is designed to get an idea of the effect size, since an estimation of the effect size is needed in order to calculate the sample size of a subsequent confirmatory study.

11.2 Determination of Sample Size

In this prospective open label study, placebo effects are likely to be present. Previous randomized controlled trials of therapy in functional gastrointestinal disorders indicate that this can be present in up to 40% of patients.(15) To compensate for this confounding factor and to demonstrate convincing

changes in perceived symptom burden at least 60% of patients should show improvement on-treatment compared to off-treatment (run-in phase). Assuming a moderate effect (Cohen's effect size of 0.4) on the primary outcome measure (effect size and standard deviation as in a previous paper by Carbone et al. (21)) power calculation suggests that 58 patients are required to detect a significant effect at a convincing level of statistical significance (beta 0.9, alpha <0.05). In the context of this study, the inclusion of 60 patients should also be sufficient to inform the design of any, future randomized, placebo-controlled study.

11.3 Statistical criteria of termination of trial

Statistical criteria for the termination of the trial are not intended.

11.4 Planned Analyses

The statistic evaluation will be performed with SPSS (IBM SPSS Statistics, NY: IBM Corp.), version 26 or higher or Graphpad Prism (MacKiev Software), version 9.3.1 or higher or higher for PC or Mac. The demographic data will be analysed with descriptive statistics as average ± standard deviation (SD) for continuous variables and with percentage of total (%) for categorical variables.

Differences between the scores from the primary and secondary endpoint variables – at baseline and after 4-weeks treatment - will be compared initially by t-test if the data is normally distributed and Wilcoxon rank sum test when data are not normally distributed. In addition, if data is normally distributed we will perform univariate and multivariate linear regression analysis in which potential covariates will be considered; confounding will be evaluated by adding these variables to the linear regression model and looking at the change of the regression coefficients. These variables will include participants age, gender, symptom severity, psychological state and gastric function (sensitivity, emptying) at baseline.

In the analysis of the primary outcome two-tailed p ≤0.05 will be considered statistically significant. Since the evaluation of the secondary endpoints is purely exploratory, other p-values will be calculated but reported without claiming significance,

Data will be transferred from the REDCap software to the statistics program Prism for evaluation, where data are password protected and only accessible to the persons involved in the study.

All analyses will be performed at Klinik Arlesheim by the research group of Prof. Dr. Mark Fox, Department of Gastroenterology, Klinik Arlesheim.

11.4.1 Datasets to be analysed, analysis populations

At the end of the study subgroups will be created. We will analyse all outcome variables age, gender, dyspepsia symptom severity (LDQ), other gastrointestinal symptoms, psychological state and gastric function (sensitivity, emptying) at baseline.

11.4.2 Primary Analysis

In the intention to treat analysis, all patients who have completed study questionnaires at baseline and after four-weeks of treatment will be included. Following covariates will be included in multivariate models: age, gender, dyspepsia symptom severity (LDQ), other gastrointestinal symptoms, psychological state and gastric function (sensitivity, emptying) at baseline.

11.4.3 Secondary Analyses

In the per protocol analysis (after four weeks), only patients who have taken at least half of the study medication will be included. Comparisons will be made between scores at study begin and scores after four weeks of treatment. Following covariates will be included in multivariate models: age, gender, dyspepsia symptom severity (LDQ), other gastrointestinal symptoms, psychological state and gastric function (sensitivity, emptying) at baseline.

11.4.4 Interim analyses

No interim analyses are planned.

11.4.5 Safety analysis

The side effects will be analysed with descriptive statistics as percentage of total (%) for categorical variables.

11.4.6 Deviation(s) from the original statistical plan

Any deviations from the original statistical plan will be justified and reported as appropriate.

11.5 Handling of missing data and drop-outs

Participants who filled out only the screening and/or only the first questionnaire (baseline) will be defined as dropouts. These dropouts will be replaced.

12. QUALITY ASSURANCE AND CONTROL

The Sponsor-Investigator is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. Every work step will be carried out and recorded accordingly.

Before the beginning of the study the PI will hold a proper training for all involved study personnel. Additionally, the staff will receive written documents concerning the study from the PI.

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

The electronic Case Report Form (eCRF, or paper equivalent if required) will comprise the participant's number, the standardised questionnaires LDQ, RDQ, IBS-SSS, HADS, PHQ, ICS, as well as socio-demographic and health-related data (Prüfbogen: Patientendaten, Gesundeheitsfragebogen), collected during screening. Additionally, outcomes of the physiological investigations detailing gastric function will be transferred in electronic form from the FAN Fischer ^{13}C Breath Analysis device to the eCRF. The Lüscher Colour Test is not validated for use on electronic media. This information will be collected and analysed manually.

Prüfbogen (13-C Atemtest) and Prüfbogen (Checkliste) will be used as paper version. In exceptional cases, Prüfbogen (Patientendaten and Gesundheitsfragebogen) can also be completed on paper.

The participants will be identifiable in the eCRF/CRF neither by name nor by initials and nor by date of birth.

Once completed, data will be entered into REDCap. Any data from paper forms will be entered using the double data entry method. The data transfer from paper into the eCRF will be done at the Clinic Arlesheim. Only persons involved in the study are allowed to make eCRF entries. It will be assured that any authorised person making a CRF entry can be identified by name.

12.1.2 Specification of source documents

The ICF and the SAE standard form are found to be source data. Data collected through questionnaires in the CRF should also be considered being source data. Furthermore, any data from the clinical information system InesKis will be transferred to REDCap and be considered source data.

12.1.3. Record keeping / archiving

All study data (electronic or on paper) will be archived for a minimum of 10 years after the study termination or premature termination of the clinical trial. Data on paper will be stored in a lockable cabinet in the research department of the Clinic Arlesheim. Digital data will be kept on the internal of the server of Clinic Arlesheim, protected by a password and archived for a minimum of 10 years.

12.2 Data management

12.2.1 Data Management System

An eCRF will be prepared at the Clinic Arlesheim by the Research Group of Prof. Dr. med. Mark Fox (Department of Gastroenterology, Clinic Arlesheim) with the REDCap software, a browser-based research data base. It is a widely used software in the academic research community. REDCap offers daily backups, basic support, and an audit trail feature for even more security.

12.2.2 Data security, access and back-up

REDCap creates automatic back-ups by the REDCap Team. Additionally, manual back-ups will be made by Prof. Dr. med. Mark Fox and stored password-protected on the local server of the Clinic Arlesheim.

12.2.3 Analysis and archiving

REDCap provides automated export procedures for seamless data downloads to statistical analysis software. Data export files will be stored password-protected on the local server of the Clinic Arlesheim. Data analysis will be archived at Clinic Arlesheim for a minimum of 10 years.

12.2.4 Electronic and central data validation

REDCap provides real-time data validation, integrity checks, and other mechanisms for ensuring data quality (e.g., double data entry). Data validation ensures that correct data type is being entered and the value is within the expected range. Commercial statistical analysis software has built-in data validation mechanisms as well.

12.3 Monitoring

Mrs Forst will be responsible for the verification of the documentation for completeness and topicality (TMF), checking the data for completeness and plausibility, source data verification and the preparation of the monitoring plan and the monitoring report. All source data and documents are accessible to the monitor and all possible questions will be answered during monitoring (see Monitoring Plan).

12.4 Audits and Inspections

Study documentation and the source data/documents are accessible to auditors/inspectors (also CEC) and questions will be answered during inspections. All involved parties will keep the participant data strictly confidential. The inspector is independent of any person involved in the study.

During the audit, the following points are checked, among others:

- Performance of the study according to the study plan,
- Validity of the data,
- Quality of the study according to GCP guidelines.

After each inspection, the investigator receives a confirmation from the person responsible for the inspection. This confirmation is kept at the study centre in the research department.

12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purpose of monitoring, audits and inspections.

The following people will have access to protocol, dataset, statistical code during and after (publication) the study:

Prof Dr med Mark Fox

Dr rer nat Daniel Krüerke

Tiffany Huber

12.6 Storage of biological material and related health data

No biological material will be collected in the current study.

13. PUBLICATION AND DISSEMINATION POLICY

Every effort will be made to publish the results of this clinical trial in a peer-reviewed journal. The publication or presentation of the results requires prior comment and approval by the PI. All publications are subject to the protection of the privacy of all patient data. Data protection is also maintained if journals wish to have the raw data submitted so that the data cannot be traced back to individuals.

14. FUNDING AND SUPPORT

14.1 Funding

The study is partly financed by the Clinic Arlesheim partly by Weleda F&E AG.

Details of the financing are set out in the relevant contracts between the Clinic Arlesheim AG and the corresponding funders.

14.2 Other Support

The IMP is provided free of charge by Weleda AG. This has also placed on record in the contract between Weleda F&E AG and the Clinic Arlesheim AG.

Financial and other support from Weleda F&E AG is linked to the following information obligation:

Weleda F&E AG undertakes to inform the Clinic Arlesheim AG immediately of any changes in content or personnel that occur in connection with the project.

The Clinic Arlesheim AG undertakes to inform Weleda F&E AG immediately of any personnel changes insofar as they affect the implementation of the project and to have these changes approved by Weleda F&E.

15. INSURANCE

The liability insurance of the Clinic Arlesheim AG will pay for any damages within the scope of the study. The insurance certificate can be found in the appendix.

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17. APPENDIX

- Standard Operating Procedure: Assessment of gastric function by ^{13}C-Breath Testing with the Nottingham Test Meal
- Questionnaires: Leuven Dyspepsia Questionnaire (LDQ), Reflux Disease Questionnaire (RDQ), Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS), Hospital Anxiety and Depression Score (HADS), Personal Health Questionnaire (PHQ15), Internal Coherence Scale (ICS), Trait autonomous Regulation (Trait aR)
- Protocol Sheet for the Recording of Lüscher Color Test (LCT) Results
- Description of Gastric Alimetry System with Investigator Brochure, FDA approval certificate and MHRA registration of conformity
- Case Report Form: Checkliste
- Cover Letter, Patient Information Sheet, Informed Consent
- Monitoring Plan (Draft)
- Contract