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Clinical Trial Protocol

Trial Code: NAT-19/GPX
EudraCT No.: 2021-002254-86 / **EU CT No.:** 2023-510195-31 / **IND No.:** 169456
Acronym: MOVE-IT
Version / Date: Integrated Clinical Trial Protocol - Final Version 3.0 / 07.10.2024
Previous Version(s):
Integrated Clinical Trial Protocol - Final Version 2.0 / 21.12.2023
Clinical Trial Protocol (original protocol) - Final Version 1.0 / 25.03.2022

Double-blind, randomised, placebo-controlled, dose-finding phase IIb trial to evaluate the efficacy, safety, and tolerability of a 12-week-treatment with Naronapride in adult participants with at least moderate idiopathic or diabetic gastroparesis

Short title: Treatment of at least moderate idiopathic or diabetic gastroparesis

Investigational drugs:	Naronapride 10/20/40 mg film-coated tablets
Reference drugs:	Naronapride placebo film-coated tablets
Indication:	Idiopathic or diabetic gastroparesis (IODG)
Phase of trial:	IIb

Sponsor:
Dr. Falk Pharma GmbH
PPD
PPD
Dept. of Clinical Research & Development
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Medical Expert

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22297 Hamburg
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Trial Coordinating Investigator (TCI):

Prof. Dr. Jan Tack
UZ Leuven gasthuisberg campus
Gastroenterology and Hepatology
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3000 Leuven
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GCP Statement: The trial will be conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements concerning Clinical Trials of participating countries including archiving of essential documents.

Confidentiality Statement: The information provided in this document is strictly confidential. It is intended for guidance of the clinical investigation and is available only for parties associated with this trial. No disclosure is allowed without prior written authorisation from Dr. Falk Pharma GmbH, except to the extent necessary to obtain informed consent from potential subjects. Once signed, the terms of this protocol are binding.

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PROTOCOL SIGNATURES

Trial Title:	Double-blind, randomised, placebo-controlled, dose-finding phase IIb trial to evaluate the efficacy, safety, and tolerability of a 12-week-treatment with Naronapride in adult participants with at least moderate idiopathic or diabetic gastroparesis
Trial Code:	NAT-19/GPX

This trial protocol has been reviewed and approved by the undersigned persons. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements concerning Clinical Trials of participating countries.

Dr. Falk Pharma GmbH (Sponsor) representatives:

Clinical Project Manager:

PPD

09.10.2024 | 15:20:57 CEST

Date

Head Clinical Research:

PPD

09.10.2024 | 16:03:30 MESZ

Date

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PROTOCOL SIGNATURES (CONTINUED)

Trial Title:	Double-blind, randomised, placebo-controlled, dose-finding phase IIb trial to evaluate the efficacy, safety, and tolerability of a 12-week-treatment with Naronapride in adult participants with at least moderate idiopathic or diabetic gastroparesis
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Dr. Falk Pharma GmbH (Sponsor) representatives (-continues-):

Managing Director:
(Science and Innovation)

PPD

09.10.2024 | 15:26:12 MESZ
Date

Drug Safety Manager:

PPD

10.10.2024 | 09:00:06 MESZ
Date

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PROTOCOL SIGNATURES (CONTINUED)

Trial Title:	Double-blind, randomised, placebo-controlled, dose-finding phase IIb trial to evaluate the efficacy, safety, and tolerability of a 12-week-treatment with Naronapride in adult participants with at least moderate idiopathic or diabetic gastroparesis
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Trial Coordinating Investigator:

PPD

10.10.2024 | 09:22:10 CEST

Date

Medical Expert:

PPD

10.10.2024 | 17:33:00 MESZ

Date

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PROTOCOL SIGNATURES (CONTINUED)

Trial Title:	Double-blind, randomised, placebo-controlled, dose-finding phase IIb trial to evaluate the efficacy, safety, and tolerability of a 12-week-treatment with Naronapride in adult participants with at least moderate idiopathic or diabetic gastroparesis
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Contract Research Organisation (CRO) representatives:

Project Manager:

PPD

09.10.2024 | 15:25:51 MESZ

Date

Biostatistician:

PPD

09.10.2024 | 15:34:46 CEST

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INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Up-to-date information on investigators and administrative structure of the trial (name and contact detail of sponsor, CRO(s), central laboratory, central pathologist, etc.) will be filed in the Trial Master File (TMF) at the Sponsor and will be provided to all trial parties separately. On site this list will be stored in the Investigator Site File (ISF).

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PROTOCOL SYNOPSIS

Title	Double-blind, randomised, placebo-controlled, dose-finding phase IIb trial to evaluate the efficacy, safety, and tolerability of a 12-week-treatment with Naronapride in adult participants with at least moderate idiopathic or diabetic gastroparesis
Trial Code	NAT-19/GPX
Acronym	MOVE-IT
Country specific trial IDs	EU: EudraCT No.:2021-002254-86 (initial) / EU CT No.: 2023-510195-31 CHE: BASEC No.: 2022-01998 / SNCTP No.: 000005549 UK: IRAS No.: 1005261 USA: IND No.: 169456 AUS: TGA No.: CT-2024-CTN-01945-1 / EC Reference No. X24-0127 & 2024/ETH060000611
Protocol Version	Integrated Clinical Trial Protocol – Final Version 3.0 / 07.10.2024
Previous Version(s)	Clinical Trial Protocol for the USA - Final Version 2.0 / 30.07.2024 Clinical Trial Protocol for AUS - Final Version 1.0 / 18.03.2024 Clinical Trial Protocol for the USA - Final Version 1.0 / 07.03.2024 Integrated Clinical Trial Protocol - Final Version 2.0 / 21.12.2023 Clinical Trial Protocol - Final Version 1.0 / 25.03.2022 (original protocol)
Protocol Amendment(s)	Integrated protocol version 3.0 / 07.10.2024 includes: Local Protocol Addendum 01 for US – Final version 1.0 / 23.01.2024 Integrated protocol version 2.0 / 21.12.2023 includes all below mentioned local protocol amendments: Local Protocol Amendment 01 for France (FR) – Final Version 1.0 / 29.03.2023 Local Protocol Amendment 02 for United Kingdom (UK) – Final Version 1.0 / 07.02.2023 Local Protocol Amendment 01 for Switzerland and United Kingdom (CHE and UK) – Final Version 1.0 / 03.06.2022 Local Protocol Amendment 01 for Germany (DE) – Final Version 1.0 / 08.05.2022
Objectives	**Primary:** • To evaluate the efficacy of a 12-week treatment with naronapride compared to placebo on disease signs and symptoms in participants with at least moderate idiopathic or diabetic gastroparesis. **Secondary:** • To determine the optimal dose-level of naronapride after completion of a 12-week treatment in participants with at least moderate idiopathic or diabetic gastroparesis, • To evaluate safety and tolerability of naronapride compared to placebo in participants with at least moderate idiopathic or diabetic gastroparesis. **Exploratory:** • To assess further effects of naronapride in participants with at least moderate idiopathic or diabetic gastroparesis.

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Phase	IIb (dose-finding)
Test drug	Naronapride 10/20/40 mg film-coated tablets
Reference drug	Naronapride placebo film-coated tablets
Auxiliary Medicinal Product	Locally sourced over the counter (OTC)-preparations against nausea (preferably dimenhydrinate, or, if not available in the respective country, alternatively cyclizine or meclozine) as rescue medication in the standard daily prescribed dose are allowed if not applied for more than 2 days per week from SCR 2 (visit 1) onwards and during the DBT phase until EOT/WD (visit 6).
Trial design	This is a double-blind, randomised, multi-centre, placebo-controlled, comparative, dose-finding phase IIb trial. The trial will be conducted with four treatment groups in the form of a parallel group comparison and will serve to compare oral treatment with naronapride 10 mg three times daily (TID) or 20 mg TID or 40 mg TID film-coated tablets vs. placebo tablets to evaluate efficacy, safety, and tolerability of naronapride compared to placebo and determine the optimal dose of naronapride in participants with idiopathic or diabetic gastroparesis. An interim analysis (IA) has been planned as an option for this trial, but only if warranted by the actual recruitment status. Recruitment will be monitored in a blinded fashion and the decision on performing the interim analysis will solely be made on blinded information. In case the IA will be performed, the trial will be performed according to a multi-arm, 2-stage, group-sequential adaptive design with the option of sample size adjustment, treatment arm selection, or early termination after the planned IA. The overall trial duration for the individual participant is estimated to be 18-24 weeks from screening to end of follow-up with maximum 8 visits. **Screening Phase (Up to 8 Weeks):** During the 2 to 8 weeks lasting screening phase, the presence and persistence of trial-entry criteria will be evaluated. Apart from one Quality of Life questionnaire, an electronic tool (ePROM) will be used in this trial for documentation of Patient Reported Outcomes Measures. It will be allowed to combine the first screening visit (SCR 1, visit 0) and the second screening visit (SCR 2, visit 1) in one single visit, provided that all assessments required for SCR 1 and SCR 2 can be performed at the same day. On date of the second screening visit (SCR 2, visit 1) at the latest, participants will receive access to this web-based tool and will be carefully instructed on how to use this tool. The interval between SCR 2 (visit 1) and the baseline visit (BSL, visit 2) should be at least 2 weeks but may be extended up to 4 weeks to ensure that all screening results are available at the time of planned randomisation at BSL (visit 2). From SCR 2 (visit 1) onwards, participants are asked to complete the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index – Daily Diary (ANMS GCSI-DD) on a daily basis. The screening assessments of gastroparesis signs and symptoms in the last week before randomisation at BSL (visit 2) will serve as the baseline values used in the analyses of the primary endpoint. **Treatment phase (12 Weeks):** At BSL (visit 2) eligible participants will be randomly assigned (1:1:1:1) to one of the three dose groups of naronapride (low, medium, high dose) or the placebo

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	group and will be stratified by type of gastroparesis to each group (66.7% idiopathic and 33.3% diabetic per group). **Group A:** Naronapride 10 mg TID **Group B:** Naronapride 20 mg TID **Group C:** Naronapride 40 mg TID **Group D:** Naronapride placebo tablets (shortly placebo tablets) TID The 12-week treatment will be in a double-blind fashion. Placebo tablets match verum tablets in shape, size, taste, and appearance. Major meals are defined as breakfast, lunch, and dinner. All participants have to keep their normal eating habits throughout the trial. CCI [redacted] **Follow-up phase (4 Weeks):** Participants will be followed up until 4 weeks after the end of the treatment phase or until 4 weeks after the withdrawal visit, as applicable. During the treatment-free follow-up phase, the recurrence of signs and symptoms of gastroparesis will be evaluated.
Trial population	Approximately 320 adult male and female participants who have been diagnosed with gastroparesis (idiopathic or diabetic) will be recruited by trial sites located in several European and non-European countries. Sites will be encouraged to recruit a diverse sample of participants in regard to age, gender, and race/ethnicity.
Inclusion criteria	Participants meeting **all** of the following criteria will be eligible for the trial: 1. Men and women between ≥18 and ≤75 years of age, 2. Able to communicate with the investigator, understand the information on the trial and has signed the informed consent form prior to screening, 3. Body Mass Index (BMI) ≥16 and <35 kg/m^2 at screening 1 (SCR 1; visit 0), 4. History of idiopathic or diabetic gastroparesis cardinal symptoms (e.g., nausea, vomiting, early satiety, postprandial fullness, bloating or upper abdominal pain) for ≥3 months prior to BSL (visit 2), 5. Evidence of delayed gastric emptying by ^{13}C-spirulina gastric emptying breath test (GEBT) for solids with gastric emptying $T_{1/2} \geq 85.33$ minutes (≥ 90th percentile of normative data) during the screening phase, 6. Average weekly total symptom score of the ANMS GCSI-DD ≥2.0 (i.e., demonstrating at least moderate severity of gastroparesis symptoms) based on the daily symptom scores recorded for at least 5 of 7 consecutive days in the week prior to BSL (visit 2), 7. Participants with a type I or type II diabetes mellitus diagnosis must have a controlled diabetes mellitus defined as HbA_{1c} ≤11% at SCR 2 (visit 1) under stable antidiabetic medication within 2 months prior to SCR 1 (visit 0) (participants may be re-screened if diabetes mellitus has been under control for at least 60 days before re-screening), 8. Exclusion of any mechanical and/or anatomical obstructions, stenosis, structural diseases, or gastric ulcers by upper gastrointestinal endoscopy during screening phase (previous endoscopic results within 12 months prior to SCR 1 (visit 0) are acceptable, if no relevant changes in patient's

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	disease status occurred since that time), 9. No evidence of intestinal stenosis as determined by an imaging technique (i.e., either abdominal sonography, magnetic resonance imaging [MRI] or imaging by computed tomography [CT] during screening phase (previous MRI/CT or sonography results within 12 months prior to SCR 1 (visit 0) are acceptable, if no relevant changes occurred in patient's disease status since that time). Note: CT to be performed only, if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK]). 10. Negative pregnancy test in women of childbearing potential <u>during</u> screening (SCR 1, visit 0: urine test and SCR 2, visit 1: serum test) and at BSL, visit 2 (urine test), 11. Women of childbearing potential agree to use a highly effective method of birth control, defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptive methods, some intrauterine devices, sexual abstinence (true abstinence means refraining from heterosexual intercourse during the entire period of the trial when it is in line with the preferred and usual lifestyle of the participant), or vasectomised partner, during the entire duration of the trial and until 4 weeks following the last dose of trial treatment. Women of non-childbearing potential (surgically sterile [i.e., hysterectomy, bilateral salpingectomy, bilateral oophorectomy], or postmenopausal with at least two years without spontaneous menses) may be included. The investigator is responsible for determining whether the participant has this adequate birth control for trial participation. <u>Note:</u> Oral hormonal contraceptive methods should be supplemented by additional use of a male condom, as the trial drug might theoretically decrease the efficacy of some hormonal contraceptive methods.
Exclusion criteria	<u>Participants meeting **any** of the following criteria will **not** be eligible for the trial:</u> 1. Participants without access to an internet-capable terminal and/or without an own e-mail address, 2. History of major gastrointestinal surgery such as gastric bypass, anti-reflux surgery, gastric per oral endoscopic myotomy (G-POEM), gastrointestinal malignancy, colectomy (haemorrhoid surgery, appendectomy or cholecystectomy, and pyloric endoscopic dilation [if conducted more than 3 months prior to BSL (visit 2) and with a diameter of dilation ≤ 20 mm] are permitted), 3. Intrapyloric botulinum toxin injection within 12 months prior to BSL (visit 2), 4. Active gastric stimulator implant, 5. Known secondary causes of gastroparesis including but not limited to Parkinson's Disease, cancer, or connective tissue diseases, 6. Presence of inflammatory bowel disease, eosinophilic oesophagitis, or reflux oesophagitis (grade C or higher), acute gastritis (chronic gastritis as long as being asymptomatic and no treatment is required will be allowed), 7. Chronic parenteral and enteral nutrition, 8. Known unresolved eating disorder (e.g., anorexia nervosa or bulimia), 9. Current presence of bezoars, 10. Previous diagnosis of cannabinoid hyperemesis syndrome (CHS) acc. to Rome IV criteria,

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	11. Chronic diarrhoea with more than three unformed, watery, or soft stools per day (in case of acute diarrhoea in the week prior to BSL (visit 2), re-screening allowed), 12. Any severe concomitant cardiovascular, endocrine, hepatic, pulmonary, gastrointestinal or psychiatric disorder, which in the opinion of the investigator might have an impact on the participant's safety and compliance in the trial or on the interpretation of the results, 13. Diabetic ketoacidosis within 4 weeks prior to SCR 1 (visit 0), 14. Nephropathy (defined as abnormal renal function with an estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2 at SCR 2 (visit 1)), 15. ALT or ALP >2.5 x upper limit of normal (ULN) at SCR 2 (visit 1), or any degree of hepatic impairment based on Child-Pugh scores (Child-Pugh A, B and C), 16. History of moderate or severe cardiovascular or cerebrovascular events: • Stroke with sequelae that affect mobility or neuropsychiatric sequelae interfering with study aims, • Brainstem infarction with potential influence on autonomic nervous system, • Coronary heart disease (CHD) grade II-IV according to the Canadian Cardiovascular Society grading of angina pectoris. Grade I (angina with strenuous or rapid or prolonged exertion) or asymptomatic CHD is allowed, • Myocardial infarction, 17. Any known or suspicion for relevant infectious diseases associated with clinical signs (e.g., AIDS defining disease, tuberculosis, hepatitis B, or hepatitis C), 18. Any treatment within three days or 5 half-lives whichever is longer prior to the screening GEBT and 2 weeks prior to BSL (visit 2) with medication that may alter gastrointestinal motility due to prokinetic/inhibiting/antiemetic effects: • Macrolide antibiotics (e.g., erythromycin), anti-malarials, anti-protozoals, anthelminthics, • Antidiarrheals and antispasmotics (e.g., butylscoplomaine), laxatives, • Opioids or cannabinoids, • Dopamine antagonists (e.g., metoclopramide, domperidone, alizapride), • 5-HT4 agonists (e.g., tegaserod, prucalopride), • 5-HT3 antagonists (e.g., tropisetron, ondansetron), • Anorectics (e.g., fenfluramine), • Systemic/oral anticholinergics (e.g., solifenacin, mebeverine); Exception: Inhaled parasympatholytics (e.g., ipratropiumbromide for COPD/Asthma) are allowed if used at standard stable doses, • Other: aprepitant, lubiprostone, scopolamine (e.g., transdermal plaster). 19. H1-receptor antihistamines of first generation (e.g., doxylamine) within 2 weeks prior to BSL (visit 2). Exception: Locally sourced OTC preparations against nausea (preferably dimenhydrinate, alternatively cyclizine or meclozine) as rescue medication in the standard daily prescribed dose are allowed if not applied for more than 2 days per week from SCR 2 (visit 1) onwards, 20. Dopamine agonists (e.g., cabergoline) within 2 weeks prior to BSL (visit 2), 21. Class I and class III antiarrhythmics (e.g., propafenone, amiodarone)

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	within 4 weeks prior to BSL (visit 2). Occasional use of local anaesthetics for infiltration anaesthesia is allowed (e.g. articaine, lidocaine), 22. (Atypic) neuroleptics (e.g., clozapine) within 4 weeks prior to BSL (visit 2), 23. Any treatment with GLP-1 analogues within 5 weeks prior to BSL (visit 2), 24. Use of any over-the-counter medication within two weeks prior to BSL (visit 2) that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin, STW5), 25. Begin of treatment or treatment more than once per week in the last 3 months prior to BSL (visit 2) with 5-HT1-receptor agonists (including but not limited to sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan), 26. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: serotonin reuptake inhibitors, H_2R antagonists, PPIs, calcium channel blockers, tricyclic antidepressants (daily intake of up to 75 mg allowed) and tetracyclic antidepressants, 27. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: systemic corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) with the exception of additional occasional use of NSAIDs for e.g., mild headache or musculoskeletal pain, 28. Any medication with known potential of clinically relevant P-gp inhibition that might lead to increased or prolonged effects of the Investigational Medicinal Product (IMP) within 2 weeks or 5-half-lives whichever is longer prior to BSL (visit 2) under careful risk-benefit analysis at the discretion of the investigator, 29. History of a malignancy except treated basal or squamous cell carcinoma of the skin or a malignancy that has been surgically removed with no recurrence within the last five years, 30. Known intolerance/hypersensitivity to the IMP or its excipients, or to drugs of similar chemical structure or pharmacological profile, 31. Known intolerance/hypersensitivity to the excipients of the GEBT (e.g., spirulina, eggs), 32. Difficulty swallowing solid food or tablets, 33. Well-founded doubt about the participant's cooperation, e.g., because of addiction to alcohol or drugs, 34. Existing or intended pregnancy or breast-feeding, 35. Participation in another clinical trial or previous participation in this trial and having received IMP within the last 30 days or ≤5 terminal elimination half-lives of previous IMP (whichever is longer) prior to SCR 1 (visit 0), 36. Dependency (as an employee or relative) to the sponsor or investigator, 37. Commitment to an institution by virtue of an order issued either by the judicial or the administrative authorities, 38. Legal incapacity or limited legal capacity. *For the USA only*: 39. Positive urine drug screening at SCR 2 (visit 1) and at BSL (visit 2) except when the result is consistent with current prescribed medication history at the discretion of the investigator (considering the permitted drugs and dosages). Subjects who fail screening may be eligible to be re-screened following discussion with the Sponsor and/or Medical Monitor (MM).

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Benefits and expected risks	Gastroparesis significantly affects the quality of life of patients through its chronic symptoms of nausea, vomiting, abdominal pain and bloating, as well as significantly increases mortality. Medical treatment of gastroparesis depends on the type and combination of signs and symptoms as well as the severity. Currently, there is no approved drug available in Europe for the treatment of patients with gastroparesis. In the United States, metoclopramide is approved for diabetic gastroparesis, but the U.S. Department of Health and Human Services Food and Drug Administration (FDA) issued a black box warning against its permanent use (> 12 weeks). As such there is a clear unmet medical need. Preclinical and clinical pharmacodynamic studies on naronapride provided evidence of both upper and lower gastrointestinal effects, as well as therapeutic effects in Phase 2 studies in patients with chronic idiopathic constipation. The data justify investigating the use of naronapride for 12-week treatment of idiopathic or diabetic gastroparesis patients with at least moderate disease severity. The present trial is expected to provide additional information on a safe and effective dose of naronapride administered to humans. Expected risks of this trial are linked with side effects of naronapride, mainly the occurrence of symptoms related to the gastrointestinal system (such as diarrhea, nausea or abdominal pain) and headache. A thorough QT trial conducted in humans has confirmed that naronapride being a selective 5-hydroxytryptamine-4 (5-HT4) receptor agonist, at doses several times greater than the anticipated daily therapeutic dose, has no effects on heart rate, PR, QRS, QT interval duration or ECG morphology, indicating that naronapride has a low potential to delay ventricular repolarisation. Nonetheless, regular ECG monitoring will be conducted during the trial in addition to the measurement of vital signs to detect potential changes in ventricular repolarisation. Moreover, results from ECG measurements and related AE-documentation will be closely monitored by an independent Data and Safety Monitoring Board (DSMB) established by the sponsor to monitor the patients' safety parameters during the trial. Diagnostic procedures like performance of upper gastrointestinal endoscopy (UGE) and abdominal sonography or MRI or computed tomography (CT, only be performed, if part of the clinical routine to detect intestinal stenosis in the respective participating country) and ^{13}C-Spirulina GEBT are used in this trial as validated diagnostic measures to confirm the diagnosis of gastroparesis and to thoroughly exclude an overlap of symptoms with other gastrointestinal disorders. Each of these diagnostic measures will be carried out by experienced physicians only such that associated risks are minimised. Blood sampling required for the trial may in addition cause discomfort or pain, and local bleeding or hematomas. With the above provisions in place, the risks associated with participating in the trial are considered low and outweighed by the benefit of a potential future oral treatment option for idiopathic and diabetic gastroparesis. The current risk profile is therefore deemed in favour of continued development of naronapride.
Sample size	The trial will be performed according to a two-stage, multi-arm, group-sequential adaptive design with possible sample size adjustment after the planned IA. The IA is planned to be carried out when the data of 192 full analysis set (FAS)-evaluable participants of the double-blind treatment (DBT) phase (i.e., after completion of the end of treatment/withdrawal [EOT/WD] visit, visit 6) are available. If the trial is continued until completion and no

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	adaptation is made at the IA, the sample size will be 320 (4 x 80) FAS-evaluable participants.
Treatment duration	The treatment duration per participant is 12 weeks. The trial duration per participant is 18-24 weeks with a total of 8 trial visits: **Screening phase (SCR)**: Up to 8 weeks Visit 0: SCR 1 (Up to 28 days prior to SCR 2) Visit 1: SCR 2 (14 – 28 days prior to BSL (visit 2) **Double-blind, randomised treatment (DBT) phase**: 12 weeks Visit 2: BSL (Day 1) Visit 3: Interim (ITR) 1 (Day 15 ± 4) Visit 4: ITR 2 (Day 29 ± 4) Visit 5: ITR 3 (Day 57 ± 4) Visit 6: EOT/WD (Day 85 ± 4 in case of regular EOT) **Follow-up (FU) phase**: 4 weeks Visit 7: Follow-up / End of Study (FU/EOS) (28 days after individual EOT/WD (visit 6); Day 112 ± 4 in case of regular EOT)
Trial duration	Estimated start of trial: 2nd quarter 2022 (first patient first visit [FPFV]) Estimated end: 2nd quarter 2025 (last patient last visit [LPLV]) The planned recruitment period is approximately 24 months, and the trial end is defined as LPLV.
Primary efficacy endpoint	• Change of the ANMS GCSI-DD average weekly total symptom score from BSL (visit 2) to EOT/WD (visit 6). *The daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) divided by 5.*
Secondary efficacy endpoints	• Change of the modified ANMS GCSI-DD average weekly total symptom score from BSL (visit 2) to EOT/WD (visit 6). *The modified daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) plus the score value for bloating divided by 6.* • Change of the composite ANMS GCSI-DD average weekly total symptom score from BSL (visit 2) to EOT/WD (visit 6). *The composite daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of only 4 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain) divided by 4.* • Change of the ANMS GCSI-DD average weekly symptom score for *nausea* from BSL (visit 2) to EOT/WD (visit 6). • Change of the ANMS GCSI-DD average weekly symptom score for *early satiety* from BSL (visit 2) to EOT/WD (visit 6). • Change of the ANMS GCSI-DD average weekly symptom score for *postprandial fullness* from BSL (visit 2) to EOT/WD (visit 6). • Change of the ANMS GCSI-DD average weekly symptom score for *upper abdominal pain* from BSL (visit 2) to EOT/WD (visit 6). • Change of the ANMS GCSI-DD average weekly symptom score for *number of vomiting episodes* from BSL (visit 2) to EOT/WD (visit 6).

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	• Change of the ANMS GCSI-DD average weekly symptom score for *bloating* from BSL (visit 2) to EOT/WD (visit 6). • Change of the ANMS GCSI-DD average weekly item score *overall severity of gastroparesis symptoms* from BSL (visit 2) to EOT/WD (visit 6). • Change of the PAGI-SYM total score from BSL (visit 2) to EOT/WD (visit 6). • Change of the GCSI total score from BSL (visit 2) to EOT/WD (visit 6). • Change in gastric emptying $T_{1/2}$ measured by GEBT from BSL (visit 2) to EOT/WD (visit 6).
Safety variables	• Adverse Events (AEs) • Vital signs (blood pressure, heart rate) and body weight • 12-lead ECG • Haematology, blood chemistry, urinalysis • Assessment of tolerability by investigator and participant
Statistical analysis	The primary objective of this trial is to evaluate the efficacy of a 12-week treatment with different doses of naronapride compared to placebo on disease signs and symptoms in participants with at least moderate idiopathic or diabetic gastroparesis. The primary efficacy variable will be subjected to a confirmatory statistical analysis ($\alpha = 0.025$, one-sided) for three test groups in the context of a multi-arm, two-stage, group-sequential adaptive trial design for testing means in many-to-one comparisons (each verum group against placebo). The planned IA that primarily aims to verify the assumptions of the sample size calculation is planned to be conducted after 60% of participants (= 192 FAS-evaluable participants) have completed their treatment, but only if warranted by the actual recruitment status. A sponsor-independent Data Monitoring Committee (IDMC) will review unblinded data at the IA and will make recommendations to the sponsor regarding: • Verifying the assumptions of the sample size calculation and continuation of the trial as planned or recalculating sample size based on the effect size estimations of the IA and based on conditional power assessments • Investigating which active treatment arm, if applicable, should be stopped after the IA • Early stopping of the trial for efficacy or futility or safety. For confirmatory hypothesis testing, the null hypotheses will be tested using the Dunnett procedure which preserves the stage-wise α-level in this many-to-one comparison. For confirmatory hypothesis testing at the final analysis, the inverse normal method of combining the p-values will be used.
Estimands	For the evaluation of the primary objective of the trial, five different estimands will be defined. All five estimands will use the patient level weekly average of the ANMS GCSI-DD total score as endpoint. The population level summary will be done over the mean changes from BSL (visit 2) to EOT/WD (visit 6). <u>Primary estimand:</u> The primary estimand will be a treatment policy estimand using all patients within the FAS and all observed values for the evaluation regardless of the

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	occurrence of an intercurrent event (ICE). The ICE of relevance is premature termination (independent of the reason for termination). Secondary estimand I: The first secondary estimand will be a hypothetical estimand, that is we assume a hypothetical population where the ICE premature termination would have not occurred regardless of the occurrence of other ICEs (i.e., completer). Secondary estimand II: The second secondary estimands will be a while-on-treatment estimand comparing the groups while the subjects took the IMP. The relevant ICE is the premature discontinuation of medication regardless of the reason of discontinuation and other ICEs. Secondary estimand III The third secondary estimand will be a without-rescue-medication estimand comparing the groups while the subjects took the IMP without using rescue medication for more than 2 days per week. The relevant ICE is the use of rescue medication on more than 2 days per week regardless of other ICEs. Secondary estimand IV: The fourth secondary estimand will be again a hypothetical estimand comparing the treatment groups in a hypothetical population where no major protocol deviations or relevant ICEs would appear that is, it will be a population as described for the per-protocol set (PPS).
Number of trial sites	Approximately 100 trial sites in several European and non-European countries (e.g. in North America and Australia)

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FLOW CHART

	ACTIVITIES		TRIAL VISITS					
	Phase		**Screening (SCR)***		**Double-blind Treatment (DBT)**			**Follow-Up (FU)**
	Visit (V) No. **Visit Name** **Day**		**0** **SCR 1** Up to 28 days prior to SCR 2	**1** **SCR 2** 14 - 28 days prior to BSL	**2** **BSL** 1	**3-5** **ITR 1-3** 15, 29, 57 (±4)	**6** **EOT/WD** 85 (±4)	**7** **FU/EOS** EOT/WD + 28 (±4)
Procedures and Assessments	Patient information and informed consent		●					
	Inclusion/exclusion criteria		●	●	●			
	Demography		●					
	Medical (case) History		●	●				
	Gastroparesis related diets		●	●	●	●	●	●
	Previous/Concomitant medication		●	●	●	●	●	●
	Vital signs; weight, height (at SCR 1 only) and BMI		●	●	●	●	●	●
	Physical examination		●		●	●	●	
	Pregnancy test (as applicable)[1]		●	●	●	●	●	●
	GEBT[2]			●[3]			●	
	Upper gastrointestinal endoscopy (UGE), if applicable[4]		●					
	Abdominal sonography, Magnetic resonance imaging (MRI) or Computed tomography (CT), if applicable[5]		●					
	Clinical Global Impression (CGI)	Severity (S)	●	●	●	●	●	●
		Change (C)				●	●	
	Assessment of tolerability by investigator						●	
	ECG (12-leads)		●		●	●	●	●
Labs	**Local lab:**	Urinalysis (local)		●	●	●	●	●
		Blood coagulation[6]	●					
		Drug screening (urine dipstick test)[#]		●	●			
	Central lab:	Haematology[7]		●	●	●	●	●
		Serum chemistry		●	●	●	●	●
		Prolactin level[8]		●			●	
		(Fasting) Glucose level[9]		●	●		●	
		HbA1c[9]		●	●		●	
		Urinary sediment[10]		●	●	●	●	●
		Blood sampling for future trial-related scientific investigations[11]			●			

- continues -

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	ACTIVITIES	TRIAL VISITS					
	Phase	**Screening (SCR)***		**Double-blind Treatment (DBT)**			**Follow-Up (FU)**
	Visit (V) No. **Visit Name** **Day**	**0** **SCR 1** Up to 28 days prior to SCR 2	**1** **SCR 2** 14 - 28 days prior to BSL	**2** **BSL** 1	**3-5** **ITR 1-3** 15, 29, 57 (±4)	**6** **EOT/WD** 85 (±4)	**7** **FU/EOS** EOT/WD + 28 (±4)
ePROM	EQ-5D-5L questionnaire			●	●	●	●
	User account setup and use instructions for ePROM		●[12]	●[12]			
	ANMS GCSI-DD		◄———	———	———	———	———►
	PAGI-SYM/GCSI			●	●	●	●
	PAGI-QoL			●		●	
	PGI-S Scale			●	●	●	●
	PGI-C Scale				●	●	
	Assessment of tolerability by participant					●	
	Diary for Use of Rescue Medication (if necessary)[13]		◄———	———	———	———►	
	Diary for Use of Other Medication not taken on a regular basis		◄———	———	———	———►	
	Diary for IMP intake and major meals			◄———	———	———►	
	Check of ePROM entries by site			●	●	●	●
	Randomisation			●			
IMP	Distribution and instructions[14]			●	●		
	Daily administration			◄———	———	———►	
	Return, drug accountability[15]				●	●	
	Compliance to IMP				●	●	
	Adverse Events	●	●	●	●	●	●
	End of Study documentation					●[16]	●
	Appointment for next visit	●	●	●	●	●	

SCR = Screening visit; BSL = Baseline visit; ITR = Interim visit; EOT = End of Treatment; WD = Withdrawal; EOS = End of Study; FU = Follow-up; V = Visit; BMI = Body mass index; GEBT = Gastric Emptying Breath Test; ECG = Electrocardiogram; RT-PCR test = Real-time reverse transcriptase-polymerase chain reaction; HbA1c = glycated haemoglobin; EQ-5D-5L = Quality of Life questionnaire developed by EuroQol Research Foundation (The Netherlands); ePROM = electronic Patient Reported Outcome Measurements incl. diaries; ANMS GCSI-DD = American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary; DD = Daily diary; PAGI-SYM = Patient Assessment of Upper Gastrointestinal Disorders - Symptom Severity Index; GCSI = Gastroparesis Cardinal Symptom Index; PAGI-QoL = Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; PGI = Patient Global Impression; IMP = Investigational medicinal product

* If it is possible to perform all required screening assessments on the same day, SCR 1 and SCR 2 can be combined as one visit. In this case, assessments scheduled for both visits do not have to be performed twice.
# For the USA only.

1 Urine test at SCR 1 (V0), at BSL (V2), all ITRs (V3 to V5), EOT/WD (V6), and FU/EOS (V7) to be performed for female patients of child-bearing potential.
Serum human chorionic gonadotropin (hCG) test at SCR 2 (V1) will be performed for all female patients below age of 60.
Note: In case SRC 1 and SRC 2 will be combined as one visit a serum pregnancy test should be performed that visit.
2 On date, GEBTs will be performed, diabetic participants must have a fasting glucose level of < 275 mg/dL (15.3 mmol/L).
3 Medications that may alter the gastrointestinal motility (e.g., erythromycin, metoclopramide, opiates, and anticholinergics) have to be stopped at least 3 days prior to GEBT at SCR 2 (V1) (within 2 weeks prior to BSL (visit 2) the latest.
4 UGE only to be performed, if no previous upper endoscopy has been performed within the last 12 months prior to SCR 1 (V0), provided that no relevant changes in disease status occurred since that time.
5 Sonography/Imaging only to be performed, if no previous sonography/imaging has been performed within the last 12 months prior to SCR 1 (V0), provided that no relevant changes in disease status occurred since that time. CT as possible imaging procedure only to be

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performed during the screening phase if part of the clinical routine in the respective participating country, e.g., not applicable for Germany, Switzerland, and United Kingdom [UK].

6 Prior to endoscopy at SCR 1 (V0), according to the routine procedure of the trial site/country.

7 Differential blood count only at BSL (V2) and EOT/WD (V6).

8 Prolactin level at SCR 2 (V1) and EOT/WD (V6) to be determined under fasting conditions, preferably at the same time.

9 Fasting glucose level and HbA1c at SCR 2 to be determined for all trial participants. At BSL(V2) and EOT/WD (V6) only to be determined for diabetic participants. For diabetic participants who are unable to come to the site in a fasting status, fasting glucose measurements taken at participant's home are acceptable.

10 Only in case of pathologic strip test results and if necessary, in the opinion of the investigator.

11 Optional only following explicit informed consent.

12 Provision of use instructions regarding completion of ANMS-CGSI-DD, diary for Use of Rescue Medication (at SCR 2, V1), diary for Use of Other Medication, and diary for IMP intake and major meals (at BSL, V2)

13 Diary for the Use of Rescue Medication

14 Distribution of IMP at BSL (V2), ITR 2 (V4) and ITR 3 (V5) (i.e., every 4 weeks) after all other activities at these visits have been completed.

15 Return of IMP at interim visits ITR 2 (V4) and ITR 3 (V5) and at EOT/WD (V6) to allow for drug account and compliance check.

16 If a patient is withdrawn prematurely during the treatment phase, a full EOT/WD (V6) visit should be carried out as soon as possible after the last use of the IMP and documented, whenever possible. Furthermore, date and reason for withdrawal should be provided.

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Appendix A: Investigator Signature Page (template)
Appendix B: List of Changes with Amendments
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TABLE OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMG	Arzneimittelgesetz (German Drug Law)
AMP	Auxiliary Medicinal Product
ANMS GCSI-DD	American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index – Daily Diary
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BSL	Baseline visit
CA	Competent Authority
CGI-S/C	Clinical Global Impression – Severity/Change
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic Obstructive Pulmonary Disease
CPMP	Committee for Proprietary Medicinal Products
CRO	Contract research organisation
CT	Computed tomography
CTIS	Clinical Trial Information System
CTR	Clinical Trials Regulation (Regulation (EU) No. 536/2014)
CYP450	Cytochrome P450 enzymes
DBT	Double-blind treatment
DILI	Drug-induced Liver Injury
DSM	Drug Safety Manager
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of study visit
EOT	End of treatment visit
ePROM	Electronic Patient Reported Outcome Measurements
EQ-VAS	Visual analogue scale developed by EuroQol Research Foundation (The Netherlands) as part of the EQ-5D-5L Questionnaire
EU CT number	European Union Clinical Trial number
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EWP	Efficacy Working Party
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FPFV	First patient first visit

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FU	Follow-up
GCP	Good Clinical Practice for trials on Medicinal Products in the European Community
GCSI	Gastroparesis Cardinal Symptom Index
GEBT	Gastric Emptying Breath Test
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
G-POEM	Gastric per oral endoscopic myotomy
HbA1c	Glycated haemoglobin
hCG	Human chorionic gonadotropin
5-HT	5-hydroxytryptamine
IA	Interim analysis
IB	Investigator's Brochure
ICE	Intercurrent event
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH GCP	ICH harmonised tripartite guideline on GCP
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IODG	Idiopathic or diabetic gastroparesis
IRB	Institutional Review Board
IRT	Interactive Response Technology
iSAP	Statistical Analysis Plan for interim analysis
ITR	Interim visit
ITT	Intention-to-treat
LOCF	Last observation carried forward
LPLV	Last patient last visit
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MMRM	Mixed Model Repeated Measure procedure
MRI	Magnetic resonance imaging
MSC	Member State concerned
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over the counter
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index
PAGI-QoL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PGI-S/C	Patient Global Impression of severity/change
P-gp	Permeability-glycoprotein
PIIC	Patient Information and Informed Consent
PPS	Per-protocol Set

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PPI	Proton Pump Inhibitor
PR, QRS, QT, RR interval	Characteristics of ECG measurement
PT	Preferred term
QC	Quality check
QoL	Quality of Life
RT-PCR	Real-time reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCR	Screening (visit)
SDV	Source data verification
SOC	System Organ Class
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischemic attack
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TID	Ter in die (three times daily)
UGE	Upper gastrointestinal endoscopy
ULN	Upper limit of normal
vs.	Versus
WD	Withdrawal
WHO	World Health Organisation
WMA	World Medical Association

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1 INTRODUCTION

1.1 Disease Background

Gastroparesis is a disorder characterized by epigastric symptoms and delayed gastric emptying or severely disturbed gastric motor function in the absence of mechanical obstruction.[1] Typical symptoms of gastroparesis include nausea, vomiting, postprandial fullness, early satiety, bloating, and upper abdominal discomfort or pain.[2, 3] Gastroparesis can be caused by a complex neuromuscular dysfunction of the gastrointestinal system, involving vagal afferents (essential for gastric accommodation of consumed food), cholinergic neurons (involved in antral contractions), inhibitory nitrergic neurons, interstitial cells of Cajal (ICCs), as well as smooth muscle cells in gastrointestinal muscles.[4-7]

The prevalence of gastroparesis is generally higher in women.[8-10] Furthermore gastroparesis through its chronic symptoms significantly affects the quality of life of patients(11, 12) and significantly increases mortality.[13]

For the majority of patients, the aetiology remains either unknown (idiopathic gastroparesis) or it occurs secondary to diabetes mellitus (diabetic gastroparesis).[6, 14] Gastroparesis can also occur after surgical interventions (postsurgical gastroparesis), due to neurological disorders, viral or bacterial infection (postinfectious gastroparesis).[6, 8]

Idiopathic and diabetic gastroparesis (IODG) are relatively similar in their clinical presentation. However, abdominal pain is more often found in patients with idiopathic gastroparesis, whereas nausea and vomiting are more prevalent and more often severe in patients with diabetic gastroparesis.[5, 6]

Due to the overlap of symptoms with other gastrointestinal disorders, correct diagnosis of gastroparesis is difficult and there is a risk for incorrect association to bowel obstruction, functional dyspepsia, irritable bowel syndrome, or peptic ulcer disease. In addition, there are substantial knowledge gaps and inconsistencies across studies. For patients presenting with symptoms such as nausea, vomiting, postprandial fullness, bloating, and abdominal pain it is recommended to start the diagnostic work-up with an upper gastrointestinal endoscopy (UGE) to exclude mechanical obstructions, followed by motility and functional examinations. To objectively assess gastric emptying, standard scintigraphy, gastric emptying breath tests utilizing ^{13}C (GEBT), and a nondigestible capsule (SmartPill) may be used as validated diagnostic measures.[15, 16] Furthermore, impaired gastric accommodation can be diagnosed with single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI). The proximal stomach size can be quantified by gastric scintiscan (after radiolabelled meal ingestion).

To date, no standardized severity grading of gastroparesis symptoms has been established.[17] Subjective symptom burden and severity can only be obtained from the patients. Validated patient-reported symptom scales are available to grade gastroparesis severity. The Patient Assessment of upper Gastrointestinal Disorders-Symptom severity index (PAGI-SYM) assesses the severity of symptoms related to gastroparesis, gastroesophageal reflux, and dyspepsia. This questionnaire has been validated and can be used to measure the symptom severity as well as efficacy of therapy[18]. The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD) assesses gastrointestinal symptoms associated with idiopathic and diabetic gastroparesis and will be completed by the patients on a daily basis. This questionnaire has been validated and can be used to measure symptom severity as well as efficacy of therapy.[19, 20]

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Treatment of gastroparesis is based on type and combination of signs and symptoms as well as severity. For gastroparesis first-line measures usually are dietary management and in diabetic patients control of blood glucose levels. Pharmacological therapies (e.g., prokinetics for stimulation gastric emptying, antiemetics for reduction of vomiting, medications for control of pain and intestinal spasms) as symptom modulators, and surgery are employed depending on type and severity of symptoms.[6, 21] Currently, there is no approved drug in Europe for the treatment of patients with gastroparesis. In the United States, metoclopramide is approved for diabetic gastroparesis, but the U.S. Department of Health and Human Services Food and Drug Administration (FDA) issued a black box warning against its permanent use (> 12 weeks).[6, 22]

The FDA demands the development of safe and effective therapies to treat patients with gastroparesis.[17] In this trial, the safety, efficacy and tolerability of a new treatment option, naronapride, for the treatment of patients with idiopathic or diabetic gastroparesis will be evaluated.

1.2 Naronapride

Naronapride (ATI-7505) is a selective 5-hydroxytryptamine-4 (5-HT4) receptor agonist being developed as a gastrointestinal (GI) prokinetic agent for the treatment of GI motility disorders. Naronapride was designed to (1) eliminate QT prolongation and cytochrome CYP450-dependent metabolism and (2) avoid significant 5-HT4 receptor-mediated increases in heart rate at therapeutically relevant doses, pharmacodynamic side effects that diminished the therapeutic potential of first-generation 5-HT4 receptor agonists such as cisapride.

Evidence of both upper and lower GI effects has been shown in preclinical and clinical pharmacodynamic studies. Therapeutic effects have also been shown in preliminary studies in patients with erosive oesophagitis, gastroesophageal reflux disease, and chronic idiopathic constipation.

Naronapride has negligible affinity for rapidly activating delayed rectifier potassium current (IKr) channels. A thorough QT (electrocardiogram [ECG] measure that describes the time between ventricular depolarisation and its repolarisation) trial conducted in humans has confirmed that naronapride, at doses several times greater than the anticipated daily therapeutic dose, has no effects on heart rate (HR), pulse rate (PR), QRS (pattern seen in an electrocardiogram that indicates the pulses in a heartbeat and their duration), QT interval durations or ECG morphology, indicating that naronapride has a low potential to delay ventricular repolarisation. Naronapride is metabolized by a combination of esterase-mediated hydrolysis and β-oxidation and does not inhibit CYP450. Therefore, naronapride has a low potential for CYP450-mediated drug-drug metabolic interactions that can alter drug effectiveness and safety.

Naronapride was found to be a substrate of the multidrug resistance protein 1 (MDR1), also known as permeability-glycoprotein (P-gp). The pharmacological significance of this interaction is unknown at this time in people who are concomitantly taking naronapride and a P-gp inhibitor.

A detailed description of naronapride can be found in the Investigator's Brochure (IB).

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1.2.1 Mode of Action

Current evidence suggests that the GI prokinetic activity of naronapride is mediated by the selective activation of intestinal 5-HT4 receptors and an inhibitory action on the dopamine D2 receptors. In this regard the mechanism of primary action resembles the mechanism of action of cisapride. However, unlike cisapride, in vitro and in vivo data show that naronapride and its metabolites have negligible affinity for IKr channels and for other important cardiac channels such as L-type calcium, potassium, and sodium channels.

A detailed description of the mode of action of naronapride can be found in the IB.

1.2.2 Toxicology

Nonclinical toxicology studies by intravenous and oral routes in rats and dogs demonstrate an acceptable safety profile but showed naronapride related histological changes in the spleen and mammary glands, cervix, and vagina after 28 days, 91 days, or 6 months of once-daily dosing in rats and transient clinical signs (soft/mucoid stools, red/swollen head areas) and mammary gland findings (lactational changes, ductal ectasia) in dogs receiving once-daily naronapride doses for periods of up to 9 months. Naronapride was negative in a standard battery of genotoxicity tests, and there were no meaningful changes observed in safety pharmacology studies evaluating hemodynamic in dogs, pulmonary function in guinea pigs, and neurobehavior in rats. There was no impairment of male fertility but a potential effect on female fertility in rats at doses of 500 mg/kg/day. Naronapride was not teratogenic in rats or rabbits.

A detailed description of the toxicology of naronapride can be found in the IB.

1.2.3 Pharmacokinetics

After administration of a single oral dose of ^{14}C-naronapride, a mean of 77 % of the dose was excreted in feces and 12 % was excreted in urine. ATI-7500, ATI-7400, ATI-7100 and quinuclinidol were metabolites of Naronapride.

The pharmacokinetics of naronapride and its metabolite ATI-7500 appear nonlinear with respect to dose. Steady state was achieved within 4–6 days following daily dosing. The terminal half-life of naronapride following multiple doses averages between 54 and 76 hours and the apparent terminal half-life for ATI-7500 is similar, averaging between 60 and 83 hours. The administration of naronapride with a high fat meal produced a 70 % decrease in rate (C_{max}) and a 40 % decrease in extent of absorption (AUC [area under the curve]).

A thorough QT study conducted in humans according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14 guidelines confirmed that naronapride, at doses several times greater than the anticipated daily therapeutic dose, has no effects on heart rate, PR, QRS, QT interval duration or ECG morphology, indicating that naronapride has a low potential to delay ventricular repolarization.

A more detailed description of pharmacokinetic properties can be found in the IB.

1.2.4 Clinical Results

More than 900 subjects have been exposed to naronapride. Naronapride has been generally well tolerated. As expected from the pharmacology of the drug, gastrointestinal disorders

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were the most frequently reported adverse event (AE) class. The most frequently reported individual AEs were diarrhoea, headache, nausea, and abdominal pain. Diarrhoea and abdominal pain had a higher frequency in the naronapride group compared to placebo.

Naronapride increased gastric and colonic motility in healthy volunteers. In Phase 2 studies in patients, naronapride increased spontaneous bowel movements and decreased the time to first bowel movement in patients with chronic idiopathic constipation and decreased gastric acid exposure to the oesophagus and increased symptom-free days of nocturnal heartburn and dyspeptic symptoms in patients with symptomatic gastroesophageal reflux disease (GERD).

A more detailed description of clinical trial results can be found in the IB.

1.3 Rationale of the Trial

Currently, there is no approved drug for the treatment of patients with gastroparesis in Europe. In the United States, metoclopramide is approved for diabetic gastroparesis, but the FDA issued a black box warning against its permanent use (> 12 weeks). This double-blind, randomised, placebo-controlled, multi-centre, comparative, dose-finding phase IIb clinical trial will serve to compare oral treatment of patients with idiopathic or diabetic gastroparesis with either 10 mg TID (3 times daily), 20 mg TID or 40 mg TID naronapride film-coated tablets vs. placebo tablets.

The mechanism of primary action of naronapride resembles the mechanism of action of cisapride. Naronapride was designed to minimize potential cardio-vascular risks to allow its permanent use in patients with gastroparesis.

Dose selection for this clinical trial is based on the results of earlier studies with naronapride.

In one study in healthy, female volunteers, the optimal dose of naronapride for promotion of gastric emptying was 20 mg TID. The lower doses studied (3 and 10 mg TID) did not demonstrate an effect on gastric emptying.[23] Naronapride efficacy and safety in patients with chronic idiopathic constipation were assessed in a previous clinical study administrating 20 mg BID (twice daily), 40 mg BID, 80 mg BID and 120 mg BID daily over 4 weeks. The 80 mg BID group had the most consistently significant primary and secondary efficacy endpoints. Though most common AEs including abdominal pain and headache appeared to be most frequent in patients who took the highest dose (120 mg BID), naronapride was overall well-tolerated in this study.

Based on these results, 3 naronapride dose regimens will be compared to placebo in this study: 10 mg TID, 20 mg TID, and 40 mg TID.

The present trial is expected to provide efficacy, tolerability, and safety data for treatment over 12 weeks in participants with idiopathic or diabetic gastroparesis. It will focus on idiopathic or diabetic gastroparesis patients with a history of cardinal symptoms persisting for three months or more prior to the BSL visit (visit 2) and of at least moderate severity. The trial will be stratified by the type of gastroparesis (2/3 idiopathic and 1/3 diabetic) for each treatment arm. As recommended by the FDA[17], only patients with at least moderate activity are to be included in order to optimise the ability to demonstrate a treatment effect.

Furthermore, the present trial should provide additional information on a safe and effective dose of naronapride administered to humans. A treatment duration of 12 weeks seems to be sufficient to detect significant changes in ANMS GCSI-DD symptom score and was recommended by the FDA[17]. A placebo arm will be included as control for the assessment

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of efficacy and safety of the trial drug and is justified as no approved drug is available for gastroparesis.

Because the ANMS GCSI-DD is used to continuously document changes in participants' disease symptoms, including a potential worsening of their disease, and is also relevant for enrolment into the treatment phase, the use of an electronic web-based instrument (ePROM) to document the ANMS GCSI-DD and other patient related outcome measures is considered mandatory in this trial. Therefore, it is deemed appropriate to include only participants who have their own e-mail address and access to an internet-capable terminal.

1.4 Benefit/Risk Assessment

Naronapride is intended for the treatment of idiopathic or diabetic gastroparesis. Gastroparesis significantly affects the quality of life of patients through its chronic symptoms of nausea, vomiting, abdominal pain and bloating,[11, 12] as well as significantly increases mortality.[13] In preclinical and clinical pharmacodynamic studies evidence of both upper and lower GI effects of naronapride has been shown, as well as therapeutic effects in Phase 2 studies in patients with chronic idiopathic constipation. The data justify investigating the use of naronapride for 12-week treatment of idiopathic or diabetic gastroparesis patients (for more information see IB).

A thorough QT trial conducted in humans according to ICH E14 guidelines[24] and related documents has confirmed that naronapride, at doses several times greater than the anticipated daily therapeutic dose, has no effects on heart rate, PR, QRS, QT interval duration or ECG morphology, indicating that naronapride has a low potential to delay ventricular repolarisation (for more information see IB). Nonetheless, regular ECG monitoring will be conducted during the trial in addition to the measurement of vital signs to detect potential changes in ventricular repolarisation. Moreover, results from ECG measurements and related AE-documentation will be closely monitored by an independent Data and Safety Monitoring Board (DSMB) established by the sponsor to monitor the patients' safety parameters during the trial (for details refer to section 7.5).

Diagnostic procedures like performance of UGE and abdominal sonography or MRI or computed tomography (CT) and ^{13}C-Spirulina GEBT are used as validated diagnostic measures to confirm the diagnosis of gastroparesis and to thoroughly exclude an overlap of symptoms with other gastrointestinal disorders. Each of these diagnostic measures will be carried out by experienced physicians only such that associated risks are minimised.

As CT is an imaging technique based on X-rays and due to the high radiation exposure during CT, pregnant women must not be examined by computer tomography. As females of childbearing potential participating in this trial must use a highly effective method of contraception during the entire trial starting with the first screening visit (SCR 1, V0) and as a pregnancy urine test is performed at date of SCR 1 (V0) it is ensured that no pregnant woman will be exposed to X-rays during the trial.

Furthermore CT in this trial will only be performed, if part of the clinical routine to detect intestinal stenosis in the respective participating country.

With the above provisions in place, the risks associated with participating in the trial are considered low and outweighed by the benefit of a potential future oral treatment option for idiopathic and diabetic gastroparesis. The current risk profile is therefore deemed in favour of continued development of naronapride.

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2 OBJECTIVES OF THE CLINICAL TRIAL

Primary:

- To evaluate the efficacy of a 12-week treatment with naronapride compared to placebo on disease signs and symptoms in participants with at least moderate idiopathic or diabetic gastroparesis.

Secondary:

- To determine the optimal dose-level of naronapride after completion of a 12-week treatment in participants with at least moderate idiopathic or diabetic gastroparesis,
- To evaluate safety and tolerability of naronapride compared to placebo in participants with at least moderate idiopathic or diabetic gastroparesis.

Exploratory:

- To assess further effects of naronapride in participants with at least moderate idiopathic or diabetic gastroparesis.

3 PATIENTS AND TRIAL SITES

3.1 Patient Selection

The Investigator should only include patients who meet all eligibility criteria, are not put at undue risk by participating in the trial and can be expected to comply with the protocol.

Eligible patients according to inclusion and exclusion criteria will be identified by search in the patient pool already available at the investigational site or will be recruited from the population seen at the investigational sites in clinical routine. The Investigator will contact potential participants when they are presenting at the site for routine treatment of their gastroparesis. In addition, investigators may ask colleagues for help in referring suitable patients for the clinical trial, using an appropriate and approved referral letter. Furthermore, advertising may be considered (once required approvals are in place for advertisements at respective sites).

The investigator will ask suitable patients whether they are interested in participating in this clinical trial.

Patients who give their written consent, meet the respective inclusion criteria and no exclusion criteria at SCR 1 (V0) will be uniquely identified by a 4-digit screening number. The screening number will be centrally allocated by the electronic case report form (eCRF) in the order of patients' screening within the whole trial. This allows identification of all the data reported for each patient/trial participant (both terms are used synonymously). The screening number is used to protect the patient's identity and in lieu of the patient's name when the investigator reports AEs and/or other trial related data.

Patients who meet all inclusion criteria and do not violate any exclusion criterion after screening will be included into the double-blind treatment phase. As further detailed in section 9.6 randomisation will be performed via Interactive Response Technology (IRT) connected to the electronic data capture (EDC) system in use. When site staff requests randomisation for an eligible patient, this patient will be allocated a randomisation number via the IRT assigning the patient to one of the treatment arms (in conformity with the central randomization list). In a second step, the IRT assigns a medication kit number (printed on

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the labels of the medication kit boxes) available on site that corresponds to the allocated treatment group. The assigned medication kit number has to be documented in the eCRF.

Screening failures and patients withdrawn from the trial retain their screening and randomisation number, as applicable. New patients must always be allocated a new screening and randomisation number.

Subjects who fail screening may be eligible to be re-screened following discussion with the Sponsor and/or Medical Monitor (MM). Re-screened patients will be allocated with a new screening number and information about re-screening should be indicated in the eCRF. The trial will be conducted in outpatients.

As trial sites will be encouraged to recruit a diverse sample of participants in regard to age, gender, and race/ethnicity, it is anticipated that the enrolled participants will reflect a distribution representative for the underlying disease.

3.1.1 Inclusion Criteria

Patients who meet **all** of the following criteria can be enrolled into the double-blind treatment phase (DBT) of the trial:

1. Men and women between ≥18 and ≤75 years of age,
2. Able to communicate with the investigator, understand the information on the trial and has signed the informed consent form prior to screening,
3. Body Mass Index (BMI) ≥16 and <35 kg/m^2 at screening 1 (SCR 1; visit 0),
4. History of idiopathic or diabetic gastroparesis cardinal symptoms (e.g., nausea, vomiting, early satiety, postprandial fullness, bloating or upper abdominal pain) for ≥3 months prior to BSL (visit 2),
5. Evidence of delayed gastric emptying by ^{13}C-spirulina gastric emptying breath test (GEBT) for solids with gastric emptying $T_{1/2} \geq 85.33$ minutes (≥ 90th percentile of normative data) during the screening phase,
6. Average weekly total symptom score of the ANMS GCSI-DD ≥2.0 (i.e., demonstrating at least moderate severity of gastroparesis symptoms) based on the daily symptom scores recorded for at least 5 of 7 consecutive days in the week prior to BSL (visit 2),
7. Participants with a type I or type II diabetes mellitus diagnosis must have a controlled diabetes mellitus defined as HbA_{1c} ≤11% at SCR 2 (visit 1) under stable antidiabetic medication within 2 months prior to SCR 1 (visit 0) (participants may be re-screened if diabetes mellitus has been under control for at least 60 days before re-screening),
8. Exclusion of any mechanical and/or anatomical obstructions, stenosis, structural diseases, or gastric ulcers by upper gastrointestinal endoscopy during screening phase (previous endoscopic results within 12 months prior to SCR 1 (visit 0) are acceptable, if no relevant changes in patient's disease status occurred since that time),
9. No evidence of intestinal stenosis as determined by an imaging technique (i.e., either abdominal sonography, magnetic resonance imaging [MRI] or imaging by computed tomography [CT] during screening phase (previous MRI/CT or sonography results within 12 months prior to SCR 1 (visit 0) are acceptable, if no relevant changes occurred in patient's disease status since that time).
   Note: CT to be performed only, if part of the clinical routine in the respective participating country, e.g., not applicable for Germany, Switzerland and United Kingdom [UK]).
10. Negative pregnancy test in women of childbearing potential during screening (SCR 1,

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visit 0: urine test and SCR 2, visit 1: serum test) and at BSL, visit 2 (urine test),
11. Women of childbearing potential agree to use a highly effective method of birth control, defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptive methods, some intrauterine devices, sexual abstinence (true abstinence means refraining from heterosexual intercourse during the entire period of the trial when it is in line with the preferred and usual lifestyle of the participant), or vasectomised partner, during the entire duration of the trial and until 4 weeks following the last dose of trial treatment. Women of non-childbearing potential (surgically sterile [i.e., hysterectomy, bilateral salpingectomy, bilateral oophorectomy], or postmenopausal with at least two years without spontaneous menses) may be included. The investigator is responsible for determining whether the participant has this adequate birth control for trial participation.
    Note: Oral hormonal contraceptive methods should be supplemented by additional use of a male condom, as the trial drug might theoretically decrease the efficacy of some hormonal contraceptive methods.

3.1.2 Exclusion Criteria

Patients who meet **any** of the following criteria are **not** allowed to be enrolled into the DBT of the trial:

1. Participants without access to an internet-capable terminal and/or without an own e-mail address,
2. History of major gastrointestinal surgery such as gastric bypass, anti-reflux surgery, gastric per oral endoscopic myotomy (G-POEM), gastrointestinal malignancy, colectomy (haemorrhoid surgery, appendectomy or cholecystectomy, and pyloric endoscopic dilation [if conducted more than 3 months prior to BSL (visit 2) and with a diameter of dilation ≤ 20 mm] are permitted),
3. Intrapyloric botulinum toxin injection within 12 months prior to BSL (visit 2),
4. Active gastric stimulator implant,
5. Known secondary causes of gastroparesis including but not limited to Parkinson's Disease, cancer, or connective tissue diseases,
6. Presence of inflammatory bowel disease, eosinophilic oesophagitis, or reflux oesophagitis (grade C or higher), acute gastritis (chronic gastritis as long as being asymptomatic and no treatment is required will be allowed),
7. Chronic parenteral and enteral nutrition,
8. Known unresolved eating disorder (e.g., anorexia nervosa or bulimia),
9. Current presence of bezoars,
10. Previous diagnosis of cannabinoid hyperemesis syndrome (CHS) acc. to Rome IV criteria,
11. Chronic diarrhoea with more than three unformed, watery, or soft stools per day (in case of acute diarrhoea in the week prior to BSL (visit 2), re-screening allowed),
12. Any severe concomitant cardiovascular, endocrine, hepatic, pulmonary, gastrointestinal or psychiatric disorder, which in the opinion of the investigator might have an impact on the participant's safety and compliance in the trial or on the interpretation of the results,
13. Diabetic ketoacidosis within 4 weeks prior to SCR 1 (visit 0),
14. Nephropathy (defined as abnormal renal function with an estimated glomerular

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filtration rate [eGFR] <30 mL/min/1.73 m^2 at SCR 2 (visit 1)),

15. ALT or ALP >2.5 x upper limit of normal (ULN) at SCR 2 (visit 1), or any degree of hepatic impairment based on Child-Pugh scores (Child-Pugh A, B and C),
16. History of moderate or severe cardiovascular or cerebrovascular events:
    - Stroke with sequelae that affect mobility or neuropsychiatric sequelae interfering with study aims,
    - Brainstem infarction with potential influence on autonomic nervous system,
    - Coronary heart disease (CHD) grade II-IV according to the Canadian Cardiovascular Society grading of angina pectoris. Grade I (angina with strenuous or rapid or prolonged exertion) or asymptomatic CHD is allowed,
    - Myocardial infarction,
17. Any known or suspicion for relevant infectious diseases associated with clinical signs (e.g., AIDS defining disease, tuberculosis, hepatitis B, or hepatitis C),
18. Any treatment within three days or 5 half-lives whichever is longer prior to the screening GEBT and 2 weeks prior to BSL (visit 2) with medication that may alter gastrointestinal motility due to prokinetic/inhibiting/antiemetic effects:
    - Macrolide antibiotics (e.g., erythromycin), anti-malarials, anti-protozoals, anthelminthics,
    - Antidiarrheals and antispasmotics (e.g., butylscoplomaine), laxatives,
    - Opioids or cannabinoids,
    - Dopamine antagonists (e.g., metoclopramide, domperidone, alizapride),
    - 5-HT4 agonists (e.g., tegaserod, prucalopride),
    - 5-HT3 antagonists (e.g., tropisetron, ondansetron),
    - Anorectics (e.g., fenfluramine),
    - Systemic/oral anticholinergics (e.g., solifenacin, mebeverine); Exception: Inhaled parasympatholytics (e.g., ipratropiumbromide for COPD/Asthma) are allowed if used at standard stable doses,
    - Other: aprepitant, lubiprostone, scopolamine (e.g., transdermal plaster).
19. H1-receptor antihistamines of first generation (e.g., doxylamine) within 2 weeks prior to BSL (visit 2).
    Exception: Locally sourced OTC preparations against nausea (preferably dimenhydrinate, alternatively cyclizine or meclozine) as rescue medication in the standard daily prescribed dose are allowed if not applied for more than 2 days per week from SCR 2 (visit 1) onwards.
20. Dopamine agonists (e.g., cabergoline) within 2 weeks prior to BSL (visit 2),
21. Class I and class III antiarrhythmics (e.g., propafenone, amiodarone) within 4 weeks prior to BSL (visit 2). Occasional use of local anaesthetics for infiltration anaesthesia is allowed (e.g. articaine, lidocaine),
22. (Atypic) neuroleptics (e.g., clozapine) within 4 weeks prior to BSL (visit 2),
23. Any treatment with GLP-1 analogues within 5 weeks prior to BSL (visit 2),
24. Use of any over-the-counter medication within two weeks prior to BSL (visit 2) that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin, STW5),
25. Begin of treatment or treatment more than once per week in the last 3 months prior to BSL (visit 2) with 5-HT1-receptor agonists (including but not limited to sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan),
26. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: serotonin reuptake inhibitors, H_2R antagonists, PPIs, calcium channel

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blockers, tricyclic antidepressants (daily intake of up to 75 mg allowed) and tetracyclic antidepressants,
27. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: systemic corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) with the exception of additional occasional use of NSAIDs for e.g., mild headache or musculoskeletal pain,
28. Any medication with known potential of clinically relevant P-gp inhibition that might lead to increased or prolonged effects of the Investigational Medicinal Product (IMP) within 2 weeks or 5-half-lives whichever is longer prior to BSL (visit 2) under careful risk-benefit analysis at the discretion of the investigator,
29. History of a malignancy except treated basal or squamous cell carcinoma of the skin or a malignancy that has been surgically removed with no recurrence within the last five years,
30. Known intolerance/hypersensitivity to the IMP or its excipients, or to drugs of similar chemical structure or pharmacological profile,
31. Known intolerance/hypersensitivity to the excipients of the GEBT (e.g., spirulina, eggs),
32. Difficulty swallowing solid food or tablets,
33. Well-founded doubt about the participant's cooperation, e.g., because of addiction to alcohol or drugs,
34. Existing or intended pregnancy or breast-feeding,
35. Participation in another clinical trial or previous participation in this trial and having received IMP within the last 30 days or ≤5 terminal elimination half-lives of previous IMP (whichever is longer) prior to SCR 1 (visit 0),
36. Dependency (as an employee or relative) to the sponsor or investigator,
37. Commitment to an institution by virtue of an order issued either by the judicial or the administrative authorities,
38. Legal incapacity or limited legal capacity.

For the USA only:

39. Positive urine drug screening at SCR 2 (visit 1) and at BSL (visit 2) except when the result is consistent with current prescribed medication history at the discretion of the investigator (considering the permitted drugs and dosages).

Subjects who fail screening may be eligible to be re-screened following discussion with the Sponsor and/or the MM.

3.2 Trial Sites

The trial will be conducted on a multinational and multi-centre basis. It is intended that the trial will take place at approximately 100 trial sites in several European and non-European countries (e.g. in North America and Australia) specialized in gastroenterology and/or diabetology, at hospitals or private practices.

3.3 Sample Size

The trial has been planned according to a two-stage, multi-arm, group-sequential adaptive design with possible sample size adjustment following an interim analysis (IA). Only if warranted by recruitment status, an IA will be carried out when the data of 192 full analysis set (FAS)-evaluable patients of the double-blind phase are available (i.e., after completion

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of the EOT/WD visit; V6). Without sample size adjustment as part of an optional interim analysis, the sample size will be 320 (4 x 80) FAS-evaluable patients.

Section 9.4 provides details of the sample size calculation.

3.4 Project Time Schedule

The originally estimated recruitment period was 24 months and was planned to start in the second quarter of 2022 ("first patient first visit", FPFV). Trial duration including screening, treatment and follow-up phase for each participant is 18-24 weeks. According to the current progress of recruitment, the clinical trial is expected to end in the second quarter of 2025. The trial end is defined as "last patient last visit" (LPLV).

4 TRIAL DESIGN

This is a double-blind, randomised, multi-centre, placebo-controlled, comparative, dose-finding phase IIb trial. The clinical trial will be conducted with four treatment groups in the form of a parallel group comparison and will serve to compare three dose groups with either 10 mg TID, 20 mg TID or 40 mg TID naronapride film-coated tablets vs. placebo film-coated tablets for the treatment of patients with idiopathic or diabetic gastroparesis.

The trial has been planned according to a multi-arm, 2-stage, group-sequential adaptive design with the option of sample size adjustment, treatment selection, or early termination in case that an IA is deemed feasible, as further detailed in section 9.3.3.

Participants stratified by type of gastroparesis will be assigned to one of the four treatment groups via a central randomisation procedure using a 1:1:1:1 balance, which could possibly shift in favour of the placebo, if one or more of the active treatment groups should be closed as a result of the optionally planned interim analysis. To guarantee the double-blinding, the trial will be conducted using placebo tablets identical in appearance, shape, size, and taste to active substance. Therefore, neither the investigator nor the patient will have knowledge of the patients' respective assignment to any of the treatment groups (A, B, C or D):

Group A: Naronapride 10 mg TID
Group B: Naronapride 20 mg TID
Group C: Naronapride 40 mg TID
Group D: Placebo TID

The overall trial duration for the individual participant is estimated to be 18-24 weeks from screening to end of follow-up with maximum 8 visits. The patients will be instructed to start the treatment with the IMP CCI [redacted] at date of the BSL visit (V2, on day 1). Treatment with the IMP will end with taking the last dose 30 minutes (15-35 minutes are considered acceptable) prior to the test meal for the GEBT at the EOT/WD visit (V6).

As stated in section 1.4, the chosen dose range, schedule, and treatment duration have been proven to be clinically safe and justifiable. Furthermore, an independent DSMB will be established to closely monitor the patients' safety parameters during the trial (see section 7.5).

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5 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

5.1 General

Dr. Falk Pharma GmbH will provide the IMP required for the clinical trial.

The IMP provided must be used only in the context of this clinical trial. Each individual medication kit and blister card or bottle with a childproof cap (for the USA only), containing the IMP is marked with a unique medication kit number (see section 5.3 for details).

Careful records will be kept of the IMP supplied to the trial sites and distributed to the patients. At the end of the study, all used and unused medication will be returned to Dr. Falk Pharma GmbH. If deficiencies of the IMP are noticed, the project manager or monitor must be informed immediately.

5.2 Characterisation of IMP

The characteristics of the IMPs (naronapride 10/20/40 mg tablets and corresponding placebo tablets) and directions for intake of the IMP are displayed in the following tables:

Table 5-1: Characteristics of naronapride film-coated tablets

Appearance	Film-coated tablets	
Composition:	Active ingredient	Naronapride 10 mg / 20 mg / 40 mg
	Excipients:	CCI [redacted]
Manufacturer:	Dr. Falk Pharma GmbH	
Mode of administration:	For oral use	
Batch no.:	NAT019-VKXX; e.g.: NAT019-VK01 (packaging campaign 1) NAT019-VK02 (packaging campaign 2) and so on.	
Storage instructions:	For clinical trial use only! Keep out of reach of children! Do not store above 25°C (77°F).	
Directions:	Take one tablet three times a day. CCI [redacted]	

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Table 5-2: Characteristics of naronapride placebo film-coated tablets

Appearance	Film-coated tablets	
Composition:	Active ingredient	None
	Excipients:	CCI [redacted]
Manufacturer:	Dr. Falk Pharma GmbH	
Mode of administration:	For oral use	
Batch no.:	NAT019-VKXX; e.g.: NAT019-VK01 (packaging campaign 1) NAT019-VK02 (packaging campaign 2) and so on.	
Storage instructions:	For clinical trial use only! Keep out of reach of children! Do not store above 25°C (77°F).	
Directions:	Take one tablet three times a day. CCI [redacted]	

All trial participants are to be instructed to keep their normal eating habits during the trial and CCI [redacted]

5.3 Packaging and Dispensing

Next Pharma is responsible for packaging and distributing the IMP.

During the 12-weeks treatment phase, a participant will receive a total of three medication kits (at BSL [V2; week 0], ITR 2 [V4; week 4], and ITR 3 [V5; week 8]), each labelled with an individual medication kit number corresponding to the randomisation number assigned at BSL (V2).

Each medication kit contains an IMP supply for 4 weeks as well as a contingency reserve of one week, either packed in blister cards with 21 naronapride/placebo tablets per blister, each sufficient for one week of treatment (three IMP/placebo tablets are needed for one day of treatment) or packed in a bottle with a childproof cap (for the USA only), containing a total of 105 tablets.

The three medication kits contain a total of 315 naronapride/placebo tablets for the treatment of one patient.

All medication kits will be supplied with a tear-off label to be stuck on the corresponding field in the drug accountability form after the IMP has been distributed to the patient.

5.4 Labelling

Labels of the IMP will be provided in English as well as in the national languages according to the respective guideline/regulation valid in each country.

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5.5 Drug Accountability

The investigator will confirm correct receipt of the IMP and ensure that the IMP is stored safely and correctly.

The IMP must be carefully stored at the trial site (in a locked area with restricted access) or at the patient's home, separately from other drugs, and kept out of the reach and sight of children. The investigator shall inform the patient about the correct storage requirements at home. The investigator will document the distribution and return of the IMP to the patient with the date, recording the quantity distributed and used on the forms provided for this purpose. The patient will be asked to return the dispensed IMP (regardless of the content of the blisters or bottles (for the USA only), respectively) at the interim visits (ITR 2 [V4] and ITR 3 [V5], only), and at the EOT/WD visit (V6), respectively. The number of tablets administered will be confirmed by counting the returned unused medication and empty blister cards or bottles returned at these visits. All trial medication as well as empty blister cards or bottles will finally be shipped to the drug supplier at the end of the trial for destruction, if not otherwise specified and agreed with the sponsor.

5.6 Concomitant Medications and Auxiliary Medicinal Products

5.6.1 Concomitant Medications

The treatment of accompanying illnesses not subject to the exclusion criteria is permissible if this is not expected to have any effect on the outcome measures used in this trial, the safety of the patient, or to interfere with the trial medication. Whenever possible, existing, permitted concomitant medication are not to be changed during the treatment phase of this trial.

As summarized in the table below, intake of the following drugs is **not permitted** during the DBT phase. During the FU phase no restrictions apply, i.e., if deemed necessary by the investigator, another therapy may be initiated to treat gastroparesis.

Table 5-3: Not permitted previous and concomitant medication

Treatment	DBT Phase (from BSL [V2] to EOT/WD [V6])
Glucagon-like peptide-1 (GLP-1) analogues	Not permitted
Any prescription medication that may alter gastrointestinal motility due to prokinetic/antiemetic effects: • Macrolide antibiotics (e.g., erythromycin), anti-malarials, anti-protozoals, anthelminthics, • Antidiarrheals and antispasmotics (e.g., butylscoplomaine), laxatives, • Opioids or cannabinoids, • Dopamine antagonists (e.g., metoclopramide, domperidone, alizapride), • 5-HT4 agonists (e.g., tegaserod, prucalopride),	Not permitted
	-continues-

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Treatment	DBT Phase (from BSL [V2] to EOT/WD [V6])
• 5-HT3 antagonists (e.g., tropisetron, ondansetron), • Anorectics (e.g., fenfluramine), • Other: aprepitant, lubiprostone, scopolamine (e.g., transdermal plaster)	
H1-receptor antihistamines of first generation (e.g., doxylamine)	Not permitted Exception: Use of dimenhydrinate alternatively cyclizine or meclozine as rescue medication (for details see section 5.6.2).
Dopamine agonists (e.g., cabergoline)	Not permitted
Class I and class III antiarrhythmics (e.g., propafenone, amiodarone)	Not permitted
(Atypic) neuroleptics (e.g., clozapine)	Not permitted
Any over the counter medication that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin, STW5)	Not permitted
Treatment with 5-HT1-receptor agonists (including but not limited to sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan)	Not permitted if taken more than once per week.
Treatment with serotonin reuptake inhibitors, H_2R antagonists, Proton Pump Inhibitors (PPIs)*, calcium channel blockers, tricyclic antidepressants (in excess of 75 mg daily) and tetracyclic antidepressants	Not permitted if not on stable dose. * Antacids containing calcium carbonate, aluminium hydroxide, or magnesium can be taken on an as-needed basis 2 hours apart from the IMP

Furthermore, the use of other IMPs within the last 4 weeks or within 5 terminal half-lives of IMP (whichever is longer) and during the clinical trial is not permitted.

If possible, **any** existing permitted concomitant medication should not be changed during the entire course of this trial. However, patients should be advised to immediately report any new medication or changes in dose of pre-existing concomitant medication to the investigator.

5.6.2 Auxiliary Medicinal Products

Locally sourced OTC-preparations against nausea (preferably dimenhydrinate, or, if not available in the respective country, alternatively cyclizine or meclozine) as rescue medication in the standard daily prescribed dose are allowed if not applied for more than 2 days per week from SCR 2 (V1) onwards and during the DBT phase until EOT/WD (V6).

5.6.3 General Provisions for Concomitant Medications and Auxiliary Medicinal Products

Previous and concomitant medication taken by patient (except for AMP/rescue medication) within 3 months prior to BSL (V2) until the end of the trial (EOS/FU, V7) must be recorded in the eCRF as well as in the patient's medical records.
Documentation should include the following:

- The type (preferably the generic name / international non-proprietary name [INN], or trade name) and route of administration,

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- The regimen including dosage schedule, daily dose, and form of application,
- The indication and duration.

Note: Each intake of AMP/rescue medication needs to be documented by patient on a daily basis in the respective section of the patient diary (see section 6.4.12.6), and needs not to be documented in the eCRF as well.

5.7 Drug-Drug Interactions

Investigators should be aware that interactions may occur during treatment with naronapride and concomitant administration of other medicinal products.

Naronapride is metabolized by a combination of esterase-mediated hydrolysis and β-oxidation and, therefore, has a low potential for CYP450-mediated drug-drug metabolic interactions that can alter drug effectiveness and safety.

Naronapride was found to be a substrate of the Multidrug resistance protein 1 (MDR1), also known as P-gp. Concomitant administration of drugs inhibiting the drug efflux pump P-gp could theoretically increase the systemic exposure of naronapride and should therefore be avoided. In case of any doubt, the investigator may contact the responsible MM or the Drug Safety Manager (DSM) of the sponsor for clarification.

Table 5-4 lists examples of clinical inhibitors of P-gp which have been shown to exert a clinically relevant inhibition. The list is not intended to be exhaustive.

Table 5-4: Clinically relevant P-gp Inhibitors

Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
Search criteria: (1) AUC fold-increase of digoxin ≥ 2 with co-administration and (2) in vitro inhibitor.

Source: Compiled by the US FDA based on a search of the University of Washington Metabolism and Transport Drug Interaction Database[25]. Search dated 26 Sep 2016/ Content current as of 03 Oct 2020 (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm).

There are no known contraindications for naronapride based on safety data from over 900 healthy volunteers and patients treated with naronapride. Additional information is provided in the corresponding IB.

5.8 Overdose

Clinical signs and symptoms of overdose are unknown. There are no reported cases of accidental or intentional overdose among clinical trial subjects and patients to date. Acute lethal dose is approximately 2000 mg/kg in rats (human equivalent dose based on body surface area=19,355 mg), 60 mg/kg/day in dogs (human equivalent dose=2,000 mg). In view of the properties of naronapride 40 mg tablets TID for 12 weeks used in this trial, an overdose resulting in toxic harm is highly unlikely. Patients suspected of receiving an overdose of naronapride should have their cardiac rhythm and blood pressure monitored, in addition to hydration and general supportive care.

Additional information is provided in the corresponding IB.

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5.9 Special precautions and warnings for use

As a recently performed in vitro study on phototoxicity does not exclude naronapride of being phototoxic in humans, patients are requested to take precautionary measures to protect their skin from sunlight (e.g., the use of sunscreens, wearing of hats and long-sleeve garments) during the treatment with naronapride and for at least 5 half-lives (corresponding to for at least 3 weeks) after taking the last dose of the IMP.

Additional information is provided in the corresponding IB.

Special attention is to be paid towards the occurrence of adverse events of special interest (AESIs), as further detailed in section 7.1.2.

6 CLINICAL TRIAL SEQUENCE

6.1 Time Sequence and Frames

The trial period for an individual patient consists of a 2 to 8 weeks lasting screening phase, a double-blind treatment phase of 12 weeks and a 4-week follow-up phase.

Table 6-1: Visit schedule

Visit		Visit no.	Day no.	Week no.	Time window [days]
SCR visit 1[1)]		V0	Up to 28 days prior to SCR visit 2		NA
SCR visit 2[1)]		V1	14 – 28 days[2)] prior to BSL visit		
BSL visit[3)]		V2	Day 1	Week 0	NA
ITR visits	ITR 1	V3	Day 15	Week 2	± 4
	ITR 2	V4	Day 29	Week 4	± 4
	ITR 3	V5	Day 57	Week 8	± 4
EOT/WD visit		V6	Day 85	Week 12	± 4
FU/EOS visit		V7	EOT/WD (V6) + 28 days	EOT/WD (V6) + 4 weeks	± 4

1) If it is possible to perform all required screening assessments on the same day, SCR 1 and SCR 2 can be combined as one visit. In this case, assessments scheduled for both visits do not have to be performed twice.

2) The interval between SCR 2 and BSL visit should be at least 2 weeks but may be extended up to 4 weeks to ensure that all screening results are available at the time of planned randomisation at BSL visit.

3) Randomisation is performed centrally via IRT.

In addition to the visits as described above, unscheduled visits, blood tests and other medical measures are possible at any time for safety reasons if deemed necessary by the investigator or medical monitor.

6.2 Overview of Time Sequence

The trial will begin with a **screening visit 1 (SCR 1; V0)**, which should take place within up to 56 days prior to the BSL visit (V2) or up to 28 days prior to the second SCR visit (SCR 2; V1), respectively. However, both visits, i.e. SCR 1 visit (V0) and SCR 2 visit (V1) might

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be combined to one visit only, in case that it will be possible to perform all necessary screening assessments in one day only. Patients who are interested in participating in the trial will be asked by the investigator after a conscientious explanation, to sign an informed consent prior to any trial-specific procedures or examinations (see section 13.1). The patient will receive written information, which outlines the sequence of events in brief and summarises the advantages and disadvantages of participation in the trial in a language that is clear and easy to understand using layman's terms.

After the patient has given his/her written consent, the trial-related screening examinations can be performed, to evaluate whether the participant is eligible for the trial.

These may include an UGE as well as an abdominal sonography or MRI or CT (CT to be performed only, if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK]) according to the usual routine at trial site, if not performed in the 12 months prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.

Screening visit 2 (SCR 2; V1) takes place 14 – 28 days before the BSL visit (V2). Specific trial-related screening examinations will be continued to further evaluate whether the patient is eligible for the trial. These include a ^{13}C-Spirulina Gastric Emptying Breath Test (GEBT) to confirm delayed gastric emptying.

Apart from one Quality of Life questionnaire (EQ-5D-5L), an electronic tool (ePROM) will be used in this trial for documentation of Patient Reported Outcomes Measures. On date of the second screening visit (SCR 2, V1) patients will receive access to this web-based tool and will be carefully instructed on how to use this tool. After appropriate instructions provided by site personnel, patients will be asked to complete the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index - Daily Diary (ANMS GCSI-DD) and the rescue medication (preferably dimenhydrinate, alternatively cyclizine or meclozine) diary (if applicable) on a daily basis. The screening assessments of gastroparesis' signs and symptoms in the last week prior to BSL visit (V2) (i.e., documentation of ANMS GCSI-DD for at least 5 of 7 consecutive days) will serve as the baseline values used in the analyses of the primary endpoint.

At the **baseline visit (BSL; V2)** a final check of the in- and exclusion criteria is to be performed. Only participants who meet **all** of inclusion criteria and **none** of the exclusion criteria can be enrolled into the double-blind treatment phase of the trial and can be allocated at random to one of the 4 treatment groups. After dispensation of the first visit kit treatment, intake of IMP will start CCI [redacted] at date of BSL (day 1, V2).

The treatment phase lasts for 12 weeks and comprises **interim visits after 2, 4 and 8 weeks (ITR 1 [V3] – ITR 3 [V5])**.

The **end of treatment (EOT)/withdrawal (WD) visit (V6)** will take place on day 85 ± 4 or at the time of participant's withdrawal.

Participants will be followed up 28 days after their last visit in the treatment phase (EOT/withdrawal visit, V6) to check for any change in the patient's health status including laboratory parameters. The **follow-up (FU)/end of study (EOS) visit (V7)** will take place at day 113 ± 4 or earlier in case a participant prematurely discontinued the double-blind treatment phase

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6.3 Description of the Clinical Trial Sequence

Note: SCR 1 (V0) and SCR 2 (V1) can be combined as one visit, if it is possible to perform all required screening assessments on the same day. In this case, assessments scheduled for both visits do not have to be performed twice.

6.3.1 Screening Visit 1 (SCR 1; V0)

Formal aspects

- Informed consent procedure, see section 13.1
- Verification of inclusion/exclusion criteria (eligibility check I), see sections 3.1.1 and 3.1.2
- Appointment for next visit

Demographic parameters and habits, see section 6.4.1

Case history (Part I), see section 6.4.2

General medical history/previous and concomitant medications

- Clinically relevant present and former diseases (other than gastroparesis), see section 6.4.2
- Previous and concomitant medication: including start dates of concomitant medication, and of all medications taken within the last 3 months prior to BSL (V2), see section 5.6.3

Examinations

- Vital signs, height, and body weight, see section 6.4.3
- Physical examination, see section 6.4.4
- 12-lead ECG, see section 6.4.10
- Urine human chorionic gonadotropin (hCG) pregnancy test (only in female participants of childbearing potential), see section 6.4.5. In case SCR 1 and SCR 2 will be combined to one visit on the same day, a serum hCG pregnancy should be performed.
- Blood sampling for local assessment of coagulation parameters prior to endoscopy (if applicable according to the routine procedure of the trial site/country), see section 6.4.6.1
- Upper gastrointestinal endoscopy (UGE), during the first two weeks of the screening phase, see section 6.4.8
- Abdominal sonography or MRI or CT (CT to be performed only, if part of the clinical routine in the respective participating country), during the first two weeks of the screening phase, see section 6.4.9
- Documentation of pre-treatment AEs, see section 7.2.1

Investigator Questionnaire(s)

- Clinical Global Impression Scale – Severity (CGI-S), see section 6.4.11.1

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6.3.2 Screening Visit 2 (SCR 2; V1)

SCR 2 (V1) to be performed **in fasting status**.

Formal aspects

- Verification of inclusion/exclusion criteria (eligibility check II), see sections 3.1.1 and 3.1.2
- Appointment for next visit

Case history (Part II)

- Up-date of case history if not completed at SCR 1 (V0), see section 6.4.2

General medical history/previous and concomitant medications

- Up-date of clinically relevant prior and concomitant diseases, see section 6.4.2
- Up-date of previous and concomitant medications, see section 5.6.3

Examinations

- Vital signs, body weight, see section 6.4.3
- Serum hCG pregnancy test (for all female patients below age of 60, see section 6.4.5)
- Blood sampling for central laboratory parameters under fasting conditions, see section 6.4.6.1
- Urine sampling for local assessment (and central laboratory assessment, if applicable), see section 6.4.6.1
- Gastric emptying breath test (GEBT), see section 6.4.7
- Documentation of pre-treatment AEs, see section 7.2.1

Investigator Questionnaires

- CGI-S, see section 6.4.11.1

ePROM (Patient Questionnaires/Daily Diaries)

- For site personnel: Set-up of patient's user account for the ePROM and provision of use instructions
- American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD Diary), see section 6.4.12.1
- Daily Diary for use of rescue medication (if necessary) [preferably dimenhydrinate, alternatively cyclizine or meclozine], see section 6.4.12.6
- Diary for use of other medication not taken on a regular basis, see section 6.4.12.7

6.3.3 Baseline Visit (BSL; V2)

For **diabetic patients** visit to be performed **in fasting status**.

Formal aspects

- Final verification of inclusion/exclusion criteria (eligibility check III, especially in regard to the average weekly total symptom score of the ANMS GCSI-DD in the last week prior to BSL (V2) and in regard to results from screening GEBT), see sections 3.1.1 and 3.1.2
- Randomisation of the patient via IRT (allocation of randomisation number and related medication kit number to be dispensed), see sections 3.1 and 9.6
    - Transfer of medication kit number assigned into the eCRF
    - If a patient will not be randomised, a primary reason (e.g., violation of in-/exclusion criteria, forbidden concomitant medication, patient's request) must be provided on the End of Study form

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- Instructions for proper handling/administration of IMP, including instructions for returning the IMP at IRT V4
- Directions for start of treatment and continued use of the IMP: The patients will be instructed to start the treatment CCI [redacted] at date of BSL (day 1) and to continue with IMP intake TID
- Dispensing of first medication kit with IMP
- Appointment for next visit

Case history (Part III); to be done prior to randomisation

- Up-date of case history if not completed during the screening phase, see section 6.4.2

Examinations

- Vital signs (blood pressure, heart rate, body temperature), body weight (BMI will be calculated in the eCRF), see section 6.4.3
- Physical examination, see section 6.4.4
- 12-lead ECG, see section 6.4.10
- Urine pregnancy test (only female patients of childbearing potential), see section 6.4.5
- Urine sampling for local assessment (and central laboratory assessment, if applicable), see section 6.4.6.1
- Blood sampling for central laboratory assessments, see section 6.4.6.1:
    - For non-diabetic participants excluding HbA1C and blood glucose level
    - For diabetic patients under fasting conditions including HbA1C and blood glucose level.
- Optional only following explicit informed consent: Blood sampling for future trial-related scientific investigations, see section 6.4.6.2
- Documentation of pre-treatment AEs (see section 7.2.1) and concomitant medication (see section 5.6.3)

Investigator's Questionnaires

- CGI-S, see section 6.4.11.1

(e)PROM (Patient Questionnaires/Daily Diaries)

- For site personnel: Check of entries since last visit and provision of further instructions to complete the ePROM as required
- PAGI-SYM including the GCSI, see sections 6.4.12.2 and 6.4.12.3
- Patient Assessment of Upper Gastrointestinal Disorders - Quality of Life (PAGI-QoL), see section 6.4.12.4
- Patient Global Impression of Severity (PGI-S), see section 6.4.12.5
- ANMS GCSI-DD Diary, see section 6.4.12.1
- Daily Diary for use of rescue medication (if necessary) [preferably dimenhydrinate, alternatively cyclizine or meclozine], see section 6.4.12.6
- Diary for use of other medication not taken on a regular basis, see section 6.4.12.7
- Daily Diary for IMP intake and major meals, see section 6.4.12.8
- EQ-5D-5L (paper-based), see section 6.4.12.10

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6.3.4 Interim Visits (ITR 1 [V3] to ITR 3 [V5])

Formal aspects

- Requesting a new visit kit number via IRT (at ITR 2 [V4] and ITR 3 [V5], only)
  - Transfer of visit kit number assigned into the eCRF
- Dispensing of IMP
- Directions for stop of treatment (at ITR 3 [V5], only): Treatment with the IMP will end with taking the last dose 30 minutes (15-35 minutes are considered acceptable) prior to the test meal for the GEBT
- Instructions for returning the IMP
- Return of IMP at IRT 2 (V4) and IRT 3 (V5)
- Compliance check by counting the IMP returned in comparison to respective diary entries for IMP intake (at ITR 2 [V4] and ITR 3 [V5], only), see section 6.4.13
- Appointment for next visit

Examinations

- Vital signs, body weight, see section 6.4.3
- Physical examination, see section 6.4.4
- 12-lead ECG, see section 6.4.10
- Urine pregnancy test (only female patients of childbearing potential) at ITR 2 (V4) and ITR 3 (V5), see section 6.4.5
- Blood and urine sampling for central and local laboratory assessments , see section 6.4.6.1
- Documentation of treatment-emergent AEs (see section 7.2.1) and concomitant medication (see section 5.6.3)
- In case of premature withdrawal from trial: date and primary reason (to be documented on the End of Study form in the eCRF), performance and documentation of the EOT/WD visit (V6), if possible.

Investigator's Questionnaires

- CGI-S, see section 6.4.11.1
- Clinical Global Impression-Change (CGI-C), see section 6.4.11.1

(e)PROM (Patient Questionnaires/Daily Diaries)

- For site personnel: Check of entries since last visit
- PAGI-SYM including the GCSI, see sections 6.4.12.2 and 6.4.12.3
- PGI-S, see section 6.4.12.5
- Patient Global Impression of Change (PGI-C), see section 6.4.12.5
- ANMS GCSI-DD Diary, see section 6.4.12.1
- Daily Diary for use of rescue medication (if necessary) [preferably dimenhydrinate, alternatively cyclizine or meclozine], see section 6.4.12.6
- Diary for use of other medication not taken on a regular basis, see section 6.4.12.7
- Daily Diary for IMP intake and major meals, see section 6.4.12.8
- EQ-5D-5L (paper-based), see section 6.4.12.10

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6.3.5 End of Treatment Visit/Withdrawal Visit (EOT/WD; V6)

EOT/WD visit (V6) to be performed **in fasting status**

Formal aspects

- Final return of IMP
- Compliance check by counting the IMP returned in comparison to respective diary entries for IMP intake, see section 6.4.13
- Appointment for next visit

Examinations

- Vital signs, body weight, see section 6.4.3
- Physical examination, see section 6.4.4
- 12-lead ECG, see section 6.4.10
- Urine pregnancy test (only female patients of childbearing potential), see section 6.4.5
- Urine sampling for local assessment (and central laboratory assessment, if applicable), see section 6.4.6.1
- Blood for central laboratory assessments, see section 6.4.6.1
- Gastric emptying breath test (GEBT) **including the intake of last dose of IMP 30 minutes (15-35 minutes are considered acceptable) prior to the test meal**, see section 6.4.7
- Documentation of treatment-emergent AEs (see section 7.2.1) and concomitant medication (see section 5.6.3)
- In case of premature withdrawal from trial: date and primary reason (to be documented on the End of Study form in the eCRF).

Investigator's Questionnaires

- CGI-S, see section 6.4.11.1
- CGI-C, see section 6.4.11.1
- Assessment of tolerability by investigator

(e)PROM (Patient Questionnaires/Daily Diaries)

- For site personnel: Check of entries since last visit
- PAGI-SYM including the GCSI, see sections 6.4.12.2 and 6.4.12.3
- PAGI-QoL, see section 6.4.12.4
- PGI-S, see section 6.4.12.5
- PGI-C, see section 6.4.12.5
- Assessment of tolerability by patient
- ANMS GCSI-DD Diary, see section 6.4.12.1
- Daily Diary for use of rescue medication (if necessary) [preferably dimenhydrinate, alternatively cyclizine or meclozine], see section 6.4.12.6
- Diary for use of other medication not taken on a regular basis, see section 6.4.12.7
- Daily Diary for IMP intake and major meals, see section 6.4.12.8
- EQ-5D-5L (paper-based), see section 6.4.12.10

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6.3.6 End of Study Visit/Follow-up Visit (EOS/FU; V7)

Formal aspects

- End of Study documentation

Examinations

- Vital signs, body weight, see section 6.4.3
- 12-lead ECG, see section 6.4.10
- Pregnancy test (only female patients of childbearing potential), see section 6.4.5
- Blood and urine sampling for central and local laboratory assessments, see section 6.4.6.1
- Documentation of post-treatment AEs (see section 7.2.1) and concomitant medication (see section 5.6.3)

Questionnaires

- CGI-S, see section 6.4.11.1

(e)PROM (Patient Questionnaires/Daily Diaries)

- For site personnel: Check of entries since last visit
- PAGI-SYM including the GCSI, see sections 6.4.12.2 and 6.4.12.3
- ANMS GCSI-DD Diary, see section 6.4.12.1
- PGI-S, see section 6.4.12.5
- EQ-5D-5L (paper-based), see section 6.4.12.10

6.4 Methods

6.4.1 Demography and habits

Demographic information to be obtained at SCR 1 (V0) will include:

- Year of birth (yyyy), age
- Gender (male, female)
- Race (Caucasian, African/African American, Asian, other [to be specified]), as described by the participant.

Patient's smoking habits (never/former/current, if current smoker number of nicotine containing units per day) and drinking habits (everyday/often/seldom/never) will also be documented at SCR 1 (V0).

6.4.2 Case history/Medical history/Gastroparesis related diets

A detailed case history of gastroparesis, as outlined below is to be documented at SCR 1 (V0) to determine patient's eligibility for study participation The case history may be updated at date of SCR 2 (V1) and/or BSL (V2) in case that additional information only becomes available until date of SCR 2 (V1) or BSL (V2):

- Date of first symptoms of gastroparesis
- Idiopathic / diabetic gastroparesis (yes/no); including date of first diagnosis.
  For diabetic gastroparesis in addition:
  - Type of diabetes mellitus (Type I/Type II) including date of first diagnosis.
- Date of last UGE (if previously performed); clinically relevant findings (if any) from previous UGE need to be documented as medical history.

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- Date of last abdominal sonography/MRI/CT (if previously performed); clinically relevant findings (if any) from previous abdominal sonography/MRI/CT need to be documented as medical history.
- Details of current and previously experienced clinical symptoms of idiopathic or diabetic gastroparesis for at least 3 months leading up to BSL (V2): nausea, vomiting, early satiety, postprandial fullness, bloating, upper abdominal pain, or others [to be specified] (yes/no))
- History of major gastrointestinal surgeries: gastric bypass, anti-reflux surgery, G-POEM, gastrointestinal malignancy, colectomy, and others [to be specified] (yes/no)

In addition, other clinically relevant prior or concomitant diseases (e.g., arterial hypertension, cardiac arrhythmia etc.) should be documented as part of the general medical history (diagnosis, start date, stop date or ongoing) at SCR 1 (V0) and should be updated at SCR 2 (V1) or BSL (V2). If any ongoing disease resolves during the course of the study the stop date should be provided.

One aspect which may have an impact on symptoms experienced by the patient is related to his/her diet. Therefore, any special diet the patient is following due to gastroparesis for the last 3 months prior to BSL (V2) and up until end of the trial (EOS/FU, V7) must be recorded in the eCRF as well as in the patient's medical records. Documentation should include the following:

- The type of diet (e.g., low fat, low fiber, no dairy products)
- The Start and stop date (if not ongoing at the time of last visit (EOS/FU, V7)

Patients should be advised to report any changes in gastroparesis related diets during the course of the study to the investigator/site personnel.

6.4.3 Vital Signs

Vital signs will be obtained at all trial visits after resting for 5 min. Vital signs will include blood pressure (systolic and diastolic in mmHg), heart rate (beats per minute [bpm]), and body temperature (°C; oral/sublingual, rectal, axillary, or auricular [preferred method]).

Height of the patient will be documented only at SCR 1 (V0). Weight of the patient will be documented at each visit. BMI [kg/m^2] will be calculated within the eCRF.

Abnormal findings in the vital signs assessed as clinically significant should be documented as medical history if noted during screening/baseline examination. Clinically significant changes from the baseline examination subsequent to the first use of IMP should be documented as AE.

6.4.4 Physical Examination

A physical examination as appropriate for the investigator will be performed at SCR 1 (V0) BSL (V2), interim visits (ITR V1 [V3] to ITR V3 [V5]) and at EOT/WD visit (V6).

If regarded as appropriate by the investigator physical examination will consist of the following body systems: 1) head including ears, nose, throat, and eyes; 2) lymphatic system; 3) endocrine system; 4) lungs and respiratory tract; 5) peripheral vascular system; 6) cardiovascular system; 7) gastrointestinal tract, liver, and spleen; 8) urogenital system;

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9) nervous system; 10) muscular and skeletal system; 11) skin and connective tissue; and 12) other.

For all body systems assessed, the actual status 'normal/abnormal, not clinically significant/abnormal, clinically significant/not done' have to be described at SCR 1 (V0). All clinically significant abnormalities should be documented as medical history if noted during screening examination. Physical examination subsequent to the first use of IMP should identify clinically significant changes from the screening examination and should be documented as AE.

6.4.5 Pregnancy Test

Female patients of childbearing potential are only eligible for the trial in case of a negative pregnancy test result during screening (SCR 1 [V0]: urine pregnancy test and SCR 2 [V1]: serum pregnancy test) and at BSL (V2) visit (urine pregnancy test).

Note: In case SRC 1 and SRC 2 will be combined as one visit a serum pregnancy test should be performed that visit.

Following information has to be collected for female patients:

- Surgically sterile (i.e., hysterectomy, bilateral salpingectomy, bilateral oophorectomy),
- Postmenopausal for at least 2 years (i.e., no menses for at least 2 years without an alternative medical cause), or
- Childbearing potential.

At SCR 2, a serum hCG pregnancy test will be performed as part of the central laboratory assessment for all female patients below age of 60. In case the serum pregnancy test result for female subjects of childbearing potential is "uncertain", the serum pregnancy re-test must be performed. Serum pregnancy test with a result "uncertain" is acceptable when a subject is surgically sterile or post-menopausal since at least 2 years.

From BSL (V2) ongoing, urine hCG pregnancy tests for female patients of childbearing potential will be repeated at each visit including the follow-up (EOS/FU, V7).

From negative pregnancy test during SCR 1 (V0) onwards and throughout the duration of the trial i.e., including the follow-up phase (until V7), female patients of childbearing potential (i.e., non-sterilised, premenopausal women) who are sexually active must use adequate contraception. Such patients will be provided with information on acceptable and unacceptable single, highly effective (Pearl-Index < 1) methods of contraception as part of the patient informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the trial.

As the trial drug might theoretically decrease the efficacy of some hormonal contraceptive methods, oral hormonal contraceptive methods should be supplemented by additional use of a male condom. For details see the below table.

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Table 6-2: Acceptable and unacceptable single highly effective (Pearl-Index < 1) methods of birth control

Acceptable single methods of birth control (Pearl-Index < 1)		**Comment**
Non-Hormonal	Total Sexual Abstinence*	Abstinence must be for the total duration of the trial and the drug washout period. Sexual abstinence should be consistent with the usual lifestyle choice of the patient or her health status.
	Vasectomised Sexual Partner	With patient's assurance that partner received post-vasectomy confirmation of azoospermia
	Bilateral Tubal Occlusion	Tubal occlusion through surgical ligation or occluding devices (e.g., Essure®) are highly effective but do not render the woman incapable of childbearing.
	Intrauterine Device (IUD)	Copper-banded coils.
Hormonal	Levonorgestrel Intrauterine System (IUS)	e.g., Mirena® coil
	Medroxyprogesterone injections	e.g., Depo-Provera®
	Etonogestrel implants	e.g., Implanon®, Norplant®
	Normal and low dose combined oral pills	This does not include tri-phasic pills.
	Norelgestromin/ethinyl estradiol transdermal system	i.e., "patches"
	Intravaginal device	e.g., oestradiol and etonogestrel containing devices such as NuvaRing®
	Cerazette® (desogestrel)	Cerazette® is currently the only highly efficacious progesterone-based pill with sufficient flexibility in its daily dose regime (i.e., 12-hour window) to be suitable for clinical trial use.
Unacceptable single methods of birth control		
Periodic sexual abstinence, coitus interruptus. Male condom, female condom, diaphragm, spermicides including double barrier methods.		

*Note: For Switzerland, sexual abstinence is no acceptable highly effective method of birth control.

Male patients who are biologically capable of having children do not need to use a special contraceptive method.

If any female patient is found to be pregnant during the treatment period of the trial (in which case trial medication must be stopped immediately) or within 28 days of last dose of trial medication, the investigator must discuss with the patient further treatment management.

The pregnancy should be reported immediately in parallel to the sponsor's DSM and to the MM of the contract research organisation (CRO) using a pregnancy notification form (see section 7.1.4 also).

If the patient agrees that her primary care physician is informed, the investigator should notify the patient's primary care physician that she was participating in a clinical trial at the

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time she became pregnant and provide details of treatment the patient received. For the unblinding procedure please refer to section 7.4.

All pregnancies will be monitored up to final outcome, using the pregnancy follow-up form. The outcome, including premature termination, must be reported to the sponsor. For details on handling and reporting of pregnancies that occur during the course of a trial refer to section 7.1.4 and section 7.2.2.

6.4.6 Laboratory Parameters

For central and local laboratory assessments a total blood volume of approximately 84 to 101 mL is to be taken during the complete trial. If necessary, for safety reasons, additional blood samples may be taken.

The central laboratory will provide investigator's lab manuals with shipping addresses and detailed handling/processing instructions; it will also provide special tubes, packaging, and labels.

6.4.6.1 Safety Assessments

The following parameters will be analysed in the **local laboratory**:

- Urine:
  - Urine strip test (Combur-9-Test; provided by the central laboratory) at SCR 2 (V1), BSL (V2), at every interim visit (ITR V1 [V3] - ITR V3 [V5]), at EOT/WD visit (V6) and EOS/FU visit (V7): protein, glucose, ketone, bilirubin, blood, urobilinogen, pH, nitrite, leucocytes
  - *For the USA only:* Urine strip test for drug screening (provided by the central laboratory) at SCR 2 (V1) and BSL (V2)
  - Urine hCG pregnancy tests (provided by the central laboratory) at SCR 1 (V0), BSL (V2) at every interim visit (ITR 1 [V3] - ITR 3 [V5]), EOT/WD visit (V6) and EOS/FU visit (V7) for female patients of childbearing potential.

  In all cases, freshly obtained midstream urine will be used to measure the urine parameters.
- Blood coagulation: – If applicable according to the routine procedure of the trial site/country to be performed prior to endoscopy at SCR 1 (V0)
  - PT (prothrombin time; % and INR [international normalised ratio]) and PTT (partial thromboplastin time)
- (Fasting) glucose level – to be performed at SCR 2 (V1) for all patients, and at BSL (V2) and at EOT/WD (V6) for diabetics only.
  - Using the fingerstick (capillary blood) technique (or alternatively the sensor technique measuring glucose in the subcutaneous tissue). Measurements using patient's own equipment are acceptable.

All other parameters will be analysed in the **central laboratory**:

- Urine:
  - Urinary sediment, only in case of pathologic urine strip test and only if regarded as necessary by the investigator, results at SCR 2 (V1), BSL (V2), at every interim visit (ITR 1 [V3] - ITR 3 [V5]), EOT/WD visit (V6) and EOS/FU visit (V7) (see also local laboratory)

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- Haematology: – to be performed at SCR 2 (V1) and at BSL (V2) to EOS/FU (V7)
  - Blood count: erythrocytes, haemoglobin, haematocrit, leucocytes including differential blood count (at BSL [V2] and EOT/WD [V6], only), mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV) and platelets
- Serum chemistry: – to be performed at SCR 2 (V1) and at BSL (V2) to EOS/FU (V7)
  - Kidney function: blood urea nitrogen (BUN), serum creatinine (to estimate glomerular filtration rate (eGFR) calculated with Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (see Levey et al., table 2)[26]
  - Liver function: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin (direct and indirect bilirubin in addition, if total bilirubin is abnormal)
  - Cholesterol (total, high-density lipoprotein [HDL], low-density lipoprotein [LDL]), triglycerides
  - Others: total protein, albumin, electrolytes (potassium, sodium, calcium, magnesia, and chloride)
  - At SCR 2 (V1) only: Serum hCG for all female patients below age of 60.
- Prolactin: – to be performed at SCR 2 (V1) and EOT/WD (V6): As prolactin shows a circadian rhythm with highest concentrations in the morning, sampling should preferably be performed at the same time in the morning under fasting conditions.
- Fasting serum glucose, glycosylated haemoglobin (HbA1c) at SCR 2 (V1) for all trial participants; for diabetic participants who are unable to come to the site in a fasting status, fasting glucose measurements taken at participant's home are acceptable as screening value. In this case participants are asked to provide their measuring results including the time of measurement and the time of their last meal. Related data need to be documented in their medical records, as well as in the eCRF.

  For non-diabetic participants no further determination of serum glucose levels and HbA1c will be necessary.

  For diabetic participants serum glucose levels and HbA1c will be measured again under fasting conditions at BSL (V2) and at EOT/WD (V6). Correspondingly respective on-site visits need to be scheduled in the morning, except for diabetics who are unable to come to the site in a fasting status. As described before, fasting glucose measurements taken at participant's home are acceptable.

The date and exact time of blood sampling for central laboratory analyses is to be documented in the patient's medical records, as well as in the eCRF.

The results of central laboratory assessments will be transferred electronically to the investigator, sponsor, and CRO in parallel on an ongoing basis and will be up-loaded in the eCRF in addition.

Printouts of the laboratory results (to be stored in the patient's medical records) will serve as source to assess abnormal laboratory values in regard to their clinical significance and causality. The results of the clinical significance and causality assessments have to be transferred to the eCRF as soon as the laboratory values are made available in the eCRF.

Laboratory results obtained during screening are relevant for the assessment of in-/exclusion criteria.

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Any clinically significant laboratory result should in addition be documented as medical history, if found prior to the first use of the IMP, or as an AE, if found during a post-baseline examination. For details refer to section 7.3.

6.4.6.2 Sampling for Future Trial-Related Scientific Investigations - Optional

Optionally, one additional full blood sample of 4 mL will be taken at BSL (V2) for future trial-related scientific investigations within the framework of the clinical development programme of naronapride, e.g., for supplementary investigations on pharmacogenetics like e.g., the analysis of polymorphisms on the serotonin reuptake transporter (SERT) gene.

The samples are planned to be archived for those possible investigations under responsibility of Dr. Falk Pharma GmbH at the central laboratory for up to 5 years after obtaining marketing authorisation of naronapride for the treatment of gastroparesis in any country worldwide (for a maximum of up to 10 years after the end of trial). In case, no marketing authorisation can be obtained, or the development program is withdrawn, samples will be destroyed immediately afterwards.

By informed consent, if applicable, patients will be informed about all relevant issues important to the patient as per GCP Guidelines and relevant national legislation. The consent process will sufficiently describe the research purposes without being over-restrictive to enable testing on collected samples in light of new scientific knowledge and technology. In case the samples shall be used for any other investigations not described adequately in the subject information previously, subjects will be informed and asked again for their consent to these investigations prior to any activities.

Blood samples for future trial-related scientific investigations will only be taken if a patient explicitly consented in written to the collection and the use of these samples for future research purposes. However, a patient may still participate in this clinical study even if he/she has not consented to additional blood sample collection.

The date and exact time of sampling is to be documented in the patient's medical records, as well as in the eCRF.

Details regarding processing, storage, and shipment of these blood samples to the central laboratory will be provided in the lab manual.

6.4.7 Gastric Emptying Breath Test (GEBT)

The GEBT, approved by the FDA in April 2015, is a non-radioactive, non-invasive, orally administered test for measuring the rate of solid phase gastric emptying (from stomach to small intestine). Performance characteristics of the GEBT compared to gastric scintigraphy are reported in Szarka et al. 2008.[27]

During this study two GEBTs will be performed, the first one at SCR 2 (V1) and the second one at EOT/WD (V6).

The GEBT at SCR 2 (V1) should be carried out at least 14 days prior to the planned BSL (V2).

Please note that patients taking any medications known to influence the rate of gastric emptying (as detailed in exclusion criterion 18) need to discontinue these medications within three days prior to the screening GEBT.

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In the exceptional case that the results of the screening GEBT are not available at the time of the scheduled BSL (V2), the period until BSL (V2) may be extended to a maximum of 28 days.

If GEBT results are not available at the end of the screening period, a patient may be re-screened. Prior to a re-screening it should be discussed with the Sponsor and/or the MM whether the results of GEBT from the initial screening can still be used or if there is the need to repeat the GEBT as part of the re-screening procedures.

For the GEBT at EOT/WD (V6) **the last dose of the IMP must be taken 30 minutes (15-35 minutes are considered acceptable) prior to the GEBT test meal** with a glass of water (100 mL). To perform both tests under the same conditions, patients should also drink 100 mL of water 30 minutes (15-35 minutes are considered acceptable) before the GEBT test meal in SCR 2 (V1).

^{13}C-Spirulina GEBT kits, packaging material for shipment, GEBT request forms and detailed instructions regarding the performance of the GEBT, handling of breath samples, and information on sample shipment are described in the GEBT user manual and will be provided to the sites.

Note: The following has to be taken into account:

- Patients are not permitted to consume solid food or liquids (including alcohol) for eight hours prior to the GEBT
- For diabetic participants fasting glucose levels of diabetic subjects should be checked before administration of GEBT and the test should only be administered to participants with a fasting glucose level of < 275 mg/dL (= 275 mg/dL x 0.0555 = 15.3 mmol/L).

Rescheduling of the GEBT within the visit window is possible if a patient does not meet all the requirements for the performance of the GEBT on the scheduled examination date.

After performing the GEBT, collected barcode labelled breath samples including a copy of the completed GEBT request form, which should list the exact times of taking the breath samples, are to be sent to the central laboratory the same day or as soon as possible after collection using the sample tube transport container. Until shipment breath samples should be stored at controlled room temperature.

When test results are ready, the investigational site will get an e-mail notification containing a link to the lab portal of the GEBT-provider from which the test results can be retrieved.

Printouts of the test results need to be stored in the patient's medical records and gastric emptying $T_{1/2}$ must be documented in the eCRF. In addition, all test results will be regularly transferred to the DM for integration of respective data into the clinical data base.

6.4.8 Upper gastrointestinal endoscopy (UGE)

An UGE within 28 days prior to the second screening visit (SCR 2, V1) that serves to exclude any mechanic and/or anatomical obstructions, stenosis, structural diseases, or gastric ulcers needs to be performed only in case that no previous UGE has been performed in the 12 months prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time. Otherwise results from previous UGE are acceptable.

The UGE is an invasive diagnostic technique to evaluate the upper gastrointestinal tract. A high-definition white light endoscope will be used to investigate oesophagus, stomach, and

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proximal duodenum and to examine the inside lining of the upper digestive system in accordance with the usual routine in each study centre.

Conscious sedation as being routinely conducted in each study centre will be performed in patients undergoing upper endoscopy under the responsibility of the gastroenterologist. Medication used for sedation needs to be documented as concomitant medication.

All clinically significant abnormalities will be documented in the medical history.

6.4.9 Abdominal Sonography or MRI or CT

To exclude intestinal stenosis an abdominal sonography, MRI, or CT (CT to be performed only, if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK]) within 28 days prior to the second screening visit (SCR 2, V1) needs to be performed only, if no previous MRI/CT imaging or sonography has been done in the last 12 month prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time. With regard to CT the relevant restrictions laid down in national laws and guidelines must be observed by the investigator.

Abdominal sonography or one of the other above mentioned imaging examinations will be performed according to the usual routine at each trial site. This includes possible procedures in preparation of the respective examination (e.g., performance in fasting status, the use of certain medications) or sedative procedures during the examination.

All clinically significant abnormalities will be documented in the medical history.

6.4.10 12-lead Electrocardiogram (ECG)

Resting 12-lead ECG recordings as a non-invasive diagnostic measurement to detect potential changes in ventricular repolarisation will be performed at SCR 1 (V0), BSL (V2) and at each subsequent visit until EOS/FU (i.e., ITR V1 [V3] to V7).

ECG recording should be taken after resting in a supine position for at least 5 min prior to recording. The following parameter will be assessed: RR-interval (s), QT-interval (ms) and QTcF-interval (ms).

Date and time (hh:mm) of the 12-lead ECG, as well as the RR-interval (s) and QT-interval (ms) and an overall interpretation of the ECG need to be recorded in the eCRF. The frequency-corrected QT interval QTc, i.e., the duration of the QT interval corrected against the RR-interval (i.e., the distance between two R-waves, indicating two subsequent heartbeats in the ECG) will automatically be calculated using the Fridericia formula (QTcF = QT time/RR interval$^{1/3}$). The interpretation of the ECG will be performed by a qualified physician of the trial team. ECG will be assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant.

Abnormal findings in the ECG assessed as clinically significant should be documented as medical history if noted during baseline examination. Clinically significant changes from the baseline examination subsequent to the first use of IMP should be documented as AE.

A copy of the print-out of the ECG will be collected by the monitor in case of abnormal findings assessed as clinically significant. Legibility must be sufficient to allow an independent review by the DSMB, established by the sponsor to closely monitor the patients' safety parameters during the trial (see section 7.5 for details). No patient name, or birth date

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must appear on the print-out; the patient must be identified only by the screening number. All original printouts (normal and abnormal) will be filed in the patient file.

6.4.11 Investigator Questionnaires

The investigator questionnaires will be part of the eCRF. These questionnaires can directly be answered in the eCRF and will be considered source data. Nonetheless the numerical value as entered in the eCRF should also be documented in the patient's medical records.

6.4.11.1 Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Change (CGI-C)

The CGI provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function.[28]

The CGI has two components - the CGI-Severity, which rates illness severity, and the CGI-Change, which rates change from the initiation (BSL, V2) of treatment.

CGI-Severity (CGI-S):

The CGI-S is based on observed and reported symptoms, behaviour, and function on a four-point scale ranging from 1 (Normal, not at all ill) to 4 (Severely ill). The CGI-S will be recorded at each study visit (SCR 1 [V0] to EOS/FU [V7]). The CGI-S asks the investigator one question:

"How would you rate the severity level of the patient's gastroparesis-related symptoms **today**?"

Table 6-3: CGI-S Scoring System

Score	Assessment	Description
1	Normal	Not at all ill, symptoms of disorder not present today
2	Mildly ill	Clearly established symptoms with minimal, if any, distress, or difficulty in social and occupational function
3	Moderately ill	Overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication
4	Severely ill	Disruptive pathology, behaviour and function are frequently influenced by symptoms, may require assistance from others

CGI-Change (CGI-C):

Each time the patient is seen after treatment with the IMP has been initiated until the end of treatment, the investigator compares the patient's overall clinical condition at each visit post-baseline (ITR 1 [V3] to EOT/WD [V6]) to the BSL visit (V2). Again, only the following one query is rated on a seven-point scale (see Table 6-4):

"Please rate the change in the patient's gastroparesis-related symptoms today, as compared to the patient's gastroparesis-related symptoms at the baseline visit?"

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Table 6-4: CGI-C Scoring System

Score	Assessment	Description
1	Very much improved	Nearly all better; good level of functioning; minimal symptoms; represents a very substantial change
2	Much improved	Notably better with significant reduction of symptoms, increase in the level of functioning but some symptoms remain
3	Minimally improved	Slightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in basic clinical status, level of care, or functional capacity
4	No change	Symptoms remain essentially unchanged
5	Minimally worse	Slightly worse but may not be clinically meaningful; may represent very little change in basic clinical status or functional capacity
6	Much worse	Clinically significant increase in symptoms and diminished functioning
7	Very much worse	Severe exacerbation of symptoms and loss of functioning

6.4.11.2 Assessment of Tolerability by Investigator

Tolerability will be classified as CCI [redacted] by investigator at the EOT/WD (V6) visit.

If assessment is CCI [redacted], the investigator should check if an AE occurred.

6.4.12 Patient Questionnaires and Patient's Diary (ePROM)

At date of SCR 2 (V1) each patient will receive an individual access to a web-based electronic Patient Reported Outcome Measurement (ePROM) tool (in local language) containing the following patient questionnaires and diaries which have to be completed either on a daily base, at patient's site visits or at patient's home as applicable:

- American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS CGSI-DD), see section 6.4.12.1,
- Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM), see section 6.4.12.2, and Gastroparesis Cardinal Symptom Index (GCSI), see section 6.4.12.3,
- Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL), see section 6.4.12.4,
- Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C), see section 6.4.12.5,
- Assessment of Tolerability by Patient, see section 6.4.12.9,
- Daily Diary for Use of Rescue Medication (preferably dimenhydrinate, alternatively cyclizine or meclozine), see section 6.4.12.6,
- Diary for Use of Other Medication not taken on a regular basis, see section 6.4.12.7,

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- Daily Diary for IMP Intake and Major Meals, see section 6.4.12.8.

The web-access will be provided by the investigator/site coordinator by creating an individual user account for the patient in the eCRF. To protect patient's confidentiality, only the investigator/site coordinator responsible for creating patient's user accounts will have access to this and details of the user registration are blinded to all Sponsor personnel and to the personnel of the trial coordinating CRO, except for the responsible monitor.

Note: To create patient's user account, a patient must have an e-mail address and must have access to an internet-capable terminal.

Details on how to create the patient's individual user account will be provided with a separate eCRF Completion Guide.

At SCR 2 (V1) the investigator or delegated person is required to thoroughly train patients in the proper use of the ePROM, emphasizing the importance of avoiding missing data. In addition, patients via their web-access, will have access to a completion guide in local language throughout the trial. This will provide detailed information on how to complete the diary and the questionnaires correctly.

In case that a patient missed to complete the diary, or a questionnaire as expected, the patient will automatically receive a notification, reminding the patient to enter the missing information.

The investigator should check the entries in the patient's diaries on a regular basis, at least during the onsite visits and will ask the patient to provide missing information retrospectively if possible. Corresponding information will be entered by the patient himself, where applicable. If the patient cannot remember, the corresponding fields in the patient's diary must be set to "unknown" or to "not done" as appropriate. Data captured via the web-based ePROM tool will be directly stored in the clinical database and need not to be transferred into the eCRF in general.

Apart from the above-mentioned PROMs all being part of the ePROM one additional paper-based QoL questionnaire, the EQ-5D-5L (see section 6.4.12.10) will be used to assess patient's generic health status.

6.4.12.1 The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary

The ANMS GCSI-DD is a self-administered patient questionnaire and contains six symptoms: nausea, early satiety, post-prandial fullness, upper abdominal pain, vomiting and bloating.

From SCR 2 visit (V1) until the EOS/FU visit (V7) patients are asked to rate the worst severity of the symptoms (except vomiting) each day over the previous 24 hours as 0 ("none"), 1 ("mild"), 2 ("moderate"), 3 ("severe") to 4 ("very severe"). For vomiting, the number of vomiting episodes (emesis) over the last 24 hours is to be recorded by the patient. In addition, overall severity of gastroparesis is to be assessed. It is recommended that the daily diary should be completed at about the same time every evening usually prior to bedtime to ensure that the diary captures the patient's experience after all meals. The overall severity of gastroparesis considers that other symptoms might impact on a patient's condition:

Instructions: These questions ask about symptoms you may have each day. Please complete the daily diary at about the same time every evening usually prior to bedtime.

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For each symptom listed below, please select the answer that best describes the worst severity of each symptom during the past 24 hours. Please be sure to answer each question.

		None (0)	Mild (1)	Moderate (2)	Severe (3)	Very severe (4)
A	Bloating (feeling like you need to loosen your clothes)					
1	Nausea (feeling sick to your stomach as if you were going to vomit or throw up)					
2	Not able to finish a normal-sized meal (for a healthy person)					
3	Feeling excessively full after meals					
4	Upper abdominal pain (above the navel)					
5	During the past 24 hours, how many episodes of vomiting did you have? _____*					
6	In thinking about your gastroparesis disorder, what was the overall severity of your gastroparesis symptoms today (during the past 24 hours)?					

*Please record the number of vomits (throwing up with food or liquid coming out) that occurred in the last 24 hours. Record zero, if you have not vomited during the past 24 hours. If you vomited, write down the number of all vomits. If you vomited once, record one. If you vomited three times during the day, record three. If you vomited three times, whether it was during the same trip to the bathroom or three separate trips, record three as the number of episodes of vomiting.

The ANMS GCSI-DD average weekly total symptom score for the last week prior to BSL (V2) which is relevant for patient's eligibility to participate in the double-blind treatment phase will also be calculated automatically and displayed in the eCRF (=average of the daily total symptom scores over the 7 days prior to BSL, excluding days with intake of rescue medication (preferably dimenhydrinate, alternatively cyclizine or meclozine) or missing days. For the calculation in the eCRF, the mean ANMS GCSI score for a single day will only be calculated if a patient has documented at least 4 of 5 core symptom items (nausea, early feeling of fullness, postprandial feeling of fullness, upper abdominal pain, number of vomiting episodes) for that day.

In addition, the ANMS GCSI-DD average weekly total symptom score will be automatically calculated for the last 7 days prior to each visit post-baseline (i.e., ITR 1 [V3] to EOS/FU [V7]) and displayed in the eCRF.

Note: The ANMS GCSI-DD average weekly total symptom score will only be displayed in the eCRF, if at least 5 reliable daily total symptom scores per week are available. Regarding the statistical analysis, the daily sum score of the ANMS GCSI-DDs and the ANMS GCSI-DD average weekly total symptom scores will be recalculated according to the rules as described in section 9.3.8.

6.4.12.2 Patient Assessment of Upper Gastrointestinal Disorders - Symptom Severity Index

The Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) was developed to assess gastrointestinal symptoms in patients with GERD (gastroesophageal reflux disease), dyspepsia, and gastroparesis. The instrument includes 20 symptom questions in six subscales: heartburn/regurgitation, fullness/early satiety, nausea/vomiting, bloating, upper abdominal pain, and lower abdominal pain.[18]

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This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please select the answer that best describes how severe the symptom has been during the past 2 weeks. If you have not experienced these symptoms, select 0. If the symptom has been very mild, select 1. If the symptom has been mild, select 2. If it has been moderate, select 3. If it has been severe, select 4. If it has been very severe, select 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

		None	**Very mild**	**Mild**	**Mode-rate**	**Severe**	**Very severe**
1	Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2	Retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3	Vomiting	0	1	2	3	4	5
4	Stomach fullness	0	1	2	3	4	5
5	Not able to finish a normal-sized meal	0	1	2	3	4	5
6	Feeling excessively full after meals	0	1	2	3	4	5
7	Loss of appetite	0	1	2	3	4	5
8	Bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9	Stomach or belly visibly larger	0	1	2	3	4	5
10	Upper abdominal (above the navel) pain	0	1	2	3	4	5
11	Upper abdominal (above the navel) discomfort	0	1	2	3	4	5
12	Lower abdominal (below the navel) pain	0	1	2	3	4	5
13	Lower abdominal (below the navel) discomfort	0	1	2	3	4	5
14	Heartburn (burning pain rising in your chest or throat) during the day	0	1	2	3	4	5
15	Heartburn (burning pain rising in your chest or throat) when lying down	0	1	2	3	4	5
							-continues

16	Feeling of discomfort inside your chest during the day	0	1	2	3	4	5
17	Feeling of discomfort inside your chest at night (during sleep time)	0	1	2	3	4	5
18	Regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	0	1	2	3	4	5

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19	Regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	0	1	2	3	4	5
20	Bitter, acid, or sour taste in your mouth	0	1	2	3	4	5

The PAGI-SYM needs to be documented at BSL (V2) and in addition at each visit until FU/EOS (V7).

6.4.12.3 Gastroparesis Cardinal Symptom Index - GCSI

The GCSI was derived from the longer PAGI-SYM instrument.

The GCSI validated in 2004 by Revicki et al[29] consists of three subscales of the PAGI-SYM, selected to measure important symptoms related to gastroparesis. These subscales are nausea/vomiting (with 3 items), postprandial fulness/early satiety (with 4 items), and bloating (with 2 items) in accordance with the first 9 items of the PAGI-SYM (section 6.4.12.2).

The GCSI total score covering the symptom severity over a two-weeks period is calculated as the average of the three symptom subscales. GCSI total score can range from 0 to 5, with higher scores reflecting greater symptom severity. If any of the three subscale scores is missing, the total score is set to missing.

6.4.12.4 Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life

PAGI-QoL is a responsive and clinically relevant instrument to assess quality of life of patients with upper gastrointestinal disorders (e.g., gastroesophageal reflux disease, dyspepsia, and gastroparesis). The questionnaire is a complementary instrument to PAGI-SYM to comprehensively measure disease specific symptoms. The questionnaire has 30 questions across 5 dimensions: Daily activities, diet and food habits, psychological well-being and distress, clothing, and relationship. The high responsiveness of the questionnaire and the good cross-cultural psychometric properties qualify the PAGI-QoL as a disease-specific Patient Reported Outcome (PRO) instrument to assess treatment efficacy in international clinical trial settings.[30, 31]

The questions ask how some of the gastrointestinal problems, the patient may be experiencing (such as pain, discomfort, or other problems) may have affected overall patient's quality of life and well-being in the past 2 weeks.

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Please answer every question by selecting the number that best represents your opinion. There are no right or wrong answers.

	During the past 2 weeks, because of your gastrointestinal problems, how often…	**None of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
1	Have you had to depend on others to do your daily activities?	0	1	2	3	4	5
2	Have you avoided performing your daily activities?	0	1	2	3	4	5
3	Have you had difficulty concentrating?	0	1	2	3	4	5
4	Has it taken you longer than usual to perform your daily activities?	0	1	2	3	4	5
5	Have you felt tired?	0	1	2	3	4	5
6	Have you lost the desire to participate in social activities such as visiting friends or relatives?	0	1	2	3	4	5
7	Have you been worried about having stomach symptoms in public?	0	1	2	3	4	5
8	Have you avoided performing physical activities or sports?	0	1	2	3	4	5
9	Have you avoided traveling?	0	1	2	3	4	5
10	Have you felt frustrated about not being able to do what you wanted to do?	0	1	2	3	4	5
11	Have you felt constricted in the clothes you wear?	0	1	2	3	4	5
12	Have you felt frustrated about not being able to dress as you wanted to?	0	1	2	3	4	5
13	Have you felt concerned about what you can and cannot eat?	0	1	2	3	4	5
14	Have you avoided certain types of foods?	0	1	2	3	4	5
15	Have you restricted eating at restaurant or at someone’s home?	0	1	2	3	4	5
16	Have you felt less enjoyment in food than usual?	0	1	2	3	4	5
17	Have you felt concerned that a change in your food habits could trigger your symptoms?	0	1	2	3	4	5
18	Have you felt frustrated about not being able to choose the food you wanted to?	0	1	2	3	4	5
19	Have you felt frustrated about not being able to choose the type of beverage you wanted to?	0	1	2	3	4	5
20	Has your relationship with your spouse or partner been disturbed?	0	1	2	3	4	5

-continues-

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During the past 2 weeks, because of your gastrointestinal problems, how often…		**None of the time**	**A little of the time**	**Some of the time**	**A good bit of the time**	**Most of the time**	**All of the time**
21	Has your relationship with your children or relatives been disturbed?	0	1	2	3	4	5
22	Has your relationship with your friends been disturbed?	0	1	2	3	4	5
23	Have you been in a bad mood?	0	1	2	3	4	5
24	Have you felt depressed?	0	1	2	3	4	5
25	Have you felt anxious?	0	1	2	3	4	5
26	Have you felt angry?	0	1	2	3	4	5
27	Have you felt irritable?	0	1	2	3	4	5
28	Have you felt discouraged?	0	1	2	3	4	5
29	Have you been stressed?	0	1	2	3	4	5
30	Have you felt helpless?	0	1	2	3	4	5

The PAGI-QoL needs to be documented twice, the first time at BSL (V2) and the second time at EOT/WD (V6).

6.4.12.5 Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C)

PGI-S

The Patient Global Impression of Severity (PGI-S) is a one-item scale designed to assess a patient's impression of disease severity. This questionnaire includes a five-point Likert scale and is based on patient's symptoms over the past week. The response options include: Normal, not at all ill; mildly ill; moderately ill; and severely ill. The scale can be used to receive response on severity to single symptoms and/or the overall status over the past week.

Please choose the response below that best describes the severity of your gastroparesis symptoms over the past week.

☐ **Normal, not at all ill**
☐ **Mildly ill**
☐ **Moderately ill**
☐ **Severely ill**
☐ **Very severely ill**

The PGI-S needs to be documented at BSL (V2) and in addition at each visit subsequent to BSL (V2) until FU/EOS (V7).

PGI-C

Like the PGI-S, the Patient Global Impression of Change (PGI-C) is also a one-item scale and is based on a five-point Likert scale. The PGI-C was designed to assess if a patient's symptoms changed. The response options include: Much improved, a little improved, no change, a little worse, and much worse.

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Please choose the response below that best describes the overall change in your gastroparesis symptoms since you started taking the study medication.

☐ **Much improved**
☐ **A little improved**
☐ **No change**
☐ **A little worse**
☐ **Much worse**

The PGI-C needs to be documented at each visit after the start of treatment until EOT/WD (V6).

6.4.12.6 Daily Diary for Intake of Rescue Medication (if applicable)

As described in section 5.6.2 participants are allowed to use dimenhydrinate (alternatively cyclizine or meclozine) in the standard prescribed dose to reduce their disease symptoms if necessary, provided that dimenhydrinate/cyclizine/meclozine is not applied for more than 2 days per week from SCR 2 (V1) onwards and during the DBT phase until EOT/WD (V6). As an additional use of dimenhydrinate/cyclizine/meclozine finally may have an impact on the efficacy results, patients are asked to document each intake of rescue medication on a daily basis answering the following questions:

- CCI

It is recommended to document the use of rescue medication (dimenhydrinate/cyclizine/meclozine) at about the same time every evening usually prior to bedtime and in parallel to the documentation of the ANMS GCSI-DD to ensure that the diary captures the patient's experience over the last 24 hours. Daily documentation of the use of rescue medication will start on date of SCR 2 visit (V1) and will end with the EOT/WD (V6).

6.4.12.7 Diary for Use of other Medication (not taken on a regular basis)

From SCR 2 visit (V1) until the EOS/FU visit (V7) patients will also be asked to document other medication (beside dimenhydrinate or cyclizine or meclozine) which is taken only as needed (e.g., headache remedies) or any new medication not pre-existing since screening/baseline (e.g., cold remedies) on a separate form, providing its name and the date of use. Long-term medication (e.g., anti-hypertensive medication) taken on a regular basis must not be documented as long as there is no dose adjustment.

Based on the information as reported by patient, the investigator should document the use of other medication as concomitant medication in the eCRF, providing the information as detailed in section 5.6.3.

6.4.12.8 Daily Diary for IMP Intake and Major Meals

During the treatment phase (from BSL [V2] until EOT/WD [V6]) the patients will be asked to document each intake of the IMP (i.e., morning, midday and evening dose including the

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time of intake) and the time of their major meals (breakfast, lunch, dinner) on a daily basis, but not more than 3 days retrospectively in the respective section of the ePROM tool.

6.4.12.9 Assessment of Tolerability by Patient

As described in section 6.4.11.2 for the investigator's assessment of tolerability, patients at the EOT/WD visit (V6) will also be asked to complete a questionnaire regarding the overall tolerability of the IMP, using the same scale as the investigator CCI [redacted] The patient's questionnaire will be available in local language and will also be part of the ePROM.

If assessment is CCI the investigator should check if an AE occurred.

6.4.12.10 EQ-5D-5L

The EQ-5D-5L developed by EuroQol Research Foundation (The Netherlands) is a standardized questionnaire for self-completing measurement of a person's generic health status.[32] The EQ-5D-5L questionnaire has two components: health state description and evaluation.

The health state description part measures health status in terms of five dimensions (5D):

- mobility,
- self-care,
- usual activities,
- pain/discomfort, and
- anxiety/depression.

Mobility dimension asks about a person's "walking ability". Self-care dimension asks about the "ability to wash or dress by oneself", and usual activities dimension measures "performance in work, study, housework, family or leisure activities". Pain/discomfort dimension asks how much pain or discomfort the person has experienced, and anxiety/depression dimension asks about level of anxiousness or depression.

Each dimension has five response levels: "no problems" (1), "slight problems" (2), "moderate problems" (3), "severe problems" (4), "unable to /extreme problems" (5).

The respondent is asked to indicate his/her health state by checking the box next to the most appropriate response level for each of the five dimensions.

In the evaluation part, the respondent's overall current health status is demonstrated using a visual analogue scale (EQ-VAS) on a 20 cm vertical scale with end points of 0 and 100: 0 corresponds to "the worst health you can imagine" and 100 to "the best health you can imagine". The EQ-VAS provides a quantitative measure of the patient's perception of their overall health.

This questionnaire will be provided as a paper version in the local language and has to be completed by patient at each visit including the follow-up (EOS/FU, V7), starting with the BSL visit (V2).

Patient's answers from the EQ-5D-5L including the numeric value as marked on the EQ-VAS have to be transferred to the eCRF by site staff and completed questionnaires need to be filed with the patient's medical records.

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6.4.13 Recording of Compliance

The person responsible for the trial medication calculates the amount of used IMP by counting the unused IMP based on returned IMPs (blister cards or bottles (for the USA only) and tablets) at ITR 2 (V4) and ITR 3 (V5) (interim count) and at EOT/WD (V6) (final count). This count will be checked versus the patient's documentation of IMP intake. If necessary, discrepancies should be clarified, if possible.

The overall results will be systematically documented on appropriate forms as well as in the eCRF.

6.4.14 Planned Treatment during the Follow-up and after the End of the Trial

As a principle, the investigator should not implement another treatment for gastroparesis after the end of treatment with the IMP, i.e., during FU phase (V6 to V7). However, if deemed clinically unavoidable at investigator' discretion, a patient may receive alternative therapies during the FU phase.

Any drug treatment which will be provided during the FU phase should be documented as concomitant medication.

After completion or early discontinuation of the present trial, patients' treatment is left to investigator's discretion.

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Events

Adverse events (AEs) will be recorded at each control visit in the patient record (source document) as well as on the eCRF.

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

- Any new diagnosis,
- Any symptom that requires medical clarification or leads to in-patient admission (surgery or accident),
- Any symptom that appears on the patient's medical records,
- Any event related in time with the intake of the trial medication and affecting the health of the patient (including laboratory value changes).

7.1.1.1 Pre-treatment Adverse Events

Pre-treatment AEs are defined as AEs with a start after signature of informed consent but prior to treatment day 1, i.e., before first IMP administration.

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7.1.1.2 Treatment-emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as any event with a start date occurring on or after treatment day 1 or, if pre-existing, worsening after treatment day 1, and occurring within the period of the 12-week treatment phase.

7.1.1.3 Post-treatment Adverse Events

Post-treatment AEs are defined as AEs with a start date after EOT/WD visit (V6) or, if pre-existing, worsening during 4 weeks after the EOT/WD visit (V7), i.e., when no trial medication is administered anymore.

7.1.2 Serious Adverse Events (SAE) and Adverse Events of Special Interest (AESI)

A serious adverse event (SAE) is any untoward medical occurrence or effect in a patient or clinical investigation subject administered a pharmaceutical product and may or may not have a suspected causal relationship to the IMP and which is serious, i.e., that at any dose:

- Results in death,
- Is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Meets the definition of other medically important conditions.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

An adverse event of special interest (AESI) is an adverse event which can be serious or non-serious and which is of scientific and medical concern specific to the product for which ongoing monitoring and rapid communication is considered appropriate. Such events may require further investigation in order to characterize and understand them.

The following adverse events are considered as being of special interest:

- QT prolongation:

A QTcF prolongation of > 450 msec for males and > 470 msec for females is considered as an AESI. In case of QTcF prolongation of > 500 msec or QTcF increase of 60 ms compared to baseline level, IMP has to be discontinued (see also section 8.1).

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- Serotonin syndrome:

A serotonin syndrome defined according to Hunter Serotonin Toxicity Criteria (Dunkley et al, 2003) is considered as an AESI, if the following applies:

1. IF (spontaneous clonus = yes) THEN serotonin toxicity =YES
2. ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
3. ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
5. ELSE IF (hypertonic = yes) AND (temperature > 38^0C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] then serotonin toxicity = YES
6. ELSE serotonin toxicity = NO

In case of serotonin syndrome, IMP has to be discontinued (see also section 8.1).

- Drug-Induced Liver Injury (DILI):

DILI is defined as a liver damage or dysfunction caused by the use of a medication, OTC, dietary supplement or herbal. In some cases, DILI is associated with hepatotoxicity. Aminotransferase (ALT or AST) levels greater than the 3 x ULN are considered as an AESI. In this case the following measures are to be taken and further data have to be obtained respectively to detect a potential DILI:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

In case of Drug-Induced Liver Injury according to FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009, IMP has to be discontinued (see also section 8.1).

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- Major Adverse Cardiovascular Events (MACE):

4-point MACE (myocardial infarction, stroke, transient ischemic attack (TIA), or angina pectoris) is considered as an AESI. In case a confirmed myocardial infarction or stroke is experienced, IMP has to be discontinued. If a patient is diagnosed with TIA or angina pectoris, further diagnostic measures to evaluate the cause of the event should be performed. Further treatment with IMP is upon decision of the investigator.

- Volume depletion associated with severe diarrhea:

Volume depletion associated with severe diarrhea (i.e., patient has signs of dehydration in the form of hypotension or even syncopal events preventing the patient from normal daily activities) is considered an AESI. Investigator should check for signs at all visits during the treatment phase.

Patients with an AESI of severe diarrhea associated with volume depletion at any time during the treatment phase will be discontinued from the IMP.

- Suicidal Ideation and Behaviour:

Clinical worsening of depression and emergence of suicidal thoughts and behavior is considered as an AESI. Patients and patients with a history of depression/mood disorder should be monitored carefully for clinical signs of a worsening of depression and the emergence of suicidal thoughts and behaviors at each visit. The patient's diary ePROs (EQ-5D-5L, PAGI-QoL) might give direct or indirect hints to such a worsening. In that case, patients should immediately discontinue IMP and contact their healthcare provider to receive appropriate treatment.

- Prolactin value above normal range at EOT:

To further investigate increased prolactin levels, values above normal range at EOT are considered as AESI.
In such cases, the investigator should further evaluate the cause of the event as follows:

  - by questioning the patient for potentially known reasons and/or
  - by checking concomitant medication and underlying diseases and/or
  - by referral to a medical specialist (e.g., gynecologist or endocrinologist) for further clarification.

If no root cause can be identified, the event should be followed-up by a prolactin re-test to assess the outcome of the event.
This re-test should be performed as part of an unscheduled visit 2 weeks after EOT. As prolactin shows a circadian rhythm with highest concentrations in the morning, sampling should preferably be performed in the morning under fasting conditions (or at the same time as for the previous test).

All AESI have to be reported in the same timely manner as an SAE (see section 7.2.2.1).

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If unintended pregnancy occurs between the first administration of the IMP (V2) and up to 28 days of last dose of IMP, pregnancy has to be reported in the same timely way as an SAE. Spontaneous miscarriages should also be reported and handled as SAEs (see section 7.1.4 for details on handling of pregnancies).

Otherwise, non-serious adverse events are all AEs that do not fall into any of the above categories.

7.1.3 Adverse (Drug) Reactions

According to ICH Topic E2A, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse (drug) reactions (A[D]Rs).

This means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (i.e., according to section 7.2.1, if the causal relationship with the trial drug is assessed as certain, probable/likely, or possible).

7.1.3.1 List of Expected Adverse (Drug) Reactions

Expected A(D)Rs following administration of naronapride tablets are provided in the current version of the IMP's IB – section 6.2 Reference Safety Information (RSI).

7.1.3.2 Unexpected Adverse (Drug) Reaction

An unexpected A(D)R is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., IB).

7.1.3.3 (Suspected) Serious Adverse Reaction

The definition of Serious Adverse Reaction (SAR) includes all SAEs where a causal relationship between SAE and IMP (at any dose) is suspected by either sponsor or investigator.

Some medical events may jeopardize the subject or may require an intervention to prevent one of the characteristics/consequences for seriousness. Such important medical events should also be considered as serious.

7.1.3.4 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) refers to SAR case reports, which are not consistent with the RSI in the current version of the IMP's IB.

7.1.4 Pregnancies

If any female patient is found to be pregnant during the treatment period of the trial (in which case IMP must be stopped immediately) or within 28 days of last dose of IMP, the investigator must discuss with the patient further treatment management. Patients who become pregnant after the first administration of the IMP and up to 28 days after the last administration of the IMP will be followed up as per protocol for safety reasons.

If the patient agrees that her primary care physician is informed, the investigator should notify the patient's primary care physician that she was participating in a clinical trial at the

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time she became pregnant and provide details of treatment the patient received. For the unblinding procedure please refer to section 7.4.

Pregnancy occurring between the first screening visit (V0) and up to 28 days of last dose of IMP has to be documented as an AE. Pregnancy occurring after the first administration of the IMP and up to 28 days after the last administration of the IMP has to be reported in the same way as an SAE (using the SAE form, see section 7.2.2), i.e., it should be reported immediately in parallel to the sponsor's DSM and to the coordinating CRO. In addition, a **pregnancy notification form** should be provided along with the SAE-report.

All pregnancies will be monitored up to final outcome (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), using the **pregnancy follow-up form**. The outcome, including premature termination, must be reported to the sponsor.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

7.1.5 Medication Errors/Misuse/Abuse

A medication error refers to any unintentional error and/or failure in the dispensing or administration of the IMP that can be harmful for a patient. Medication errors include accidental overdose or underdose, inappropriate schedule of product administration, incorrect route of product administration, wrong product administered, and expired or quality diminished product administered.

Treatment non-compliance (incl. missed doses) where no clinical consequence occurred should not be recorded as medication errors.

Medication errors, misuse or abuse in relation to the IMP should be documented as AE by the investigator and notified to the sponsor.

In addition, any clinical consequences of the medication error, misuse or abuse must be recorded as separate AEs. If the AE originating from the medication error, misuse or abuse qualifies as an SAE, expedited reporting is required.

7.2 Documentation and Reporting

A condition (e.g., abnormal physical examination finding, abnormal laboratory finding, any symptom or disease) which is detected during screening or baseline examination and for which it is reasonable to assume that this condition already started prior to signing the ICF will be documented as concomitant disease in the 'Medical history and Concomitant Diseases' section of the eCRF. The same applies to conditions not related to any trial-related procedures (e.g., common cold) prior to the first administration of the IMP. Conditions in relation to trial-related procedures (like blood sampling) have to be reported as AEs and will be assessed as pre-treatment AEs.
All other events reported as AEs, will be either assessed as TEAEs or post-treatment AEs, according to the definitions provided in section 7.1.1.

7.2.1 Documentation and Reporting of Adverse Events

AEs will be recorded in the patient's medical records (source document), as well as in the eCRF.

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The patients will be instructed to contact the investigator immediately during the trial (from signature of informed consent) and until 4 weeks after EOT/WD visit, if any event occurs that might need appropriate action.

The investigator must check the patients' diaries and other patient related documents with respect to possible AEs.

Moreover, the investigator must ask at each visit starting with the BSL visit (V2) a non-suggestive question (i.e., without searching for any special symptoms), e.g.: "Has your state of health worsened since we last met?". If the answer to this question is "no", no further questions will be asked. If the answer to the question is "yes", the investigator documents the nature, time, severity, seriousness, and duration as well as the causality of the AE.

The AE term should be reported in standard medical terminology when possible.

If possible, a diagnosis should preferably be entered as the AE term rather than signs or symptoms of an event. If a diagnosis changes over time, the event term should be modified accordingly. Any worsening in severity or frequency of a concomitant disease or any new disease diagnosed in the trial after the first use of the IMP must be documented as an AE. Worsening changes in severity grade does not constitute a new entry in the CRF. It is expected that the maximum achieved severity of an AE will be assigned to it and documented in the database of the AEs.

Intermittent AEs will only be recorded once, as long as the severity does not change and 'intermittent' is added to the verbatim text of the AE term. If, however, the AE changes from intermittent to continuous, the record of the original event should be entered as terminated and restarted as a new AE.

Any procedure by itself does not constitute a reportable event but only the underlying condition leading to the procedure.

The following has to be documented for each AE:

- Nature of the event (description of symptoms and/or diagnosis),
- Seriousness,
- Severity,
- Duration of the AE: Date and time (if relevant) of onset and end,
- Frequency,
- Interval between last administration of the IMP and the onset of the AE,
- Causality assessment including information on de-challenge and re-challenge,
- Action taken with regard to IMP (none, withdrawn, not applicable),
- Treatment of the AE:
  - Concomitant intervention or procedure (e.g., diagnostic measures),
  - Concomitant medication: product (generic name / international non-proprietary name [INN]), indication, dosage, dosage interval, presentation, mode of administration, administration regimen,
- Outcome,

Seriousness for definition, see section 7.1.2

Severity is evaluated as follows:

1. **Mild:** Event/symptom does not interfere with normal daily activities
2. **Moderate:** Event/symptom interferes with normal daily activities
3. **Severe:** Event/symptom prevents normal daily activities

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Frequency is evaluated as follows:

1. Isolated (once)
2. Intermittent
3. Continuous (lasting)
4. Unknown

Causality

The relationship between an AE and the trial medication is classified according to the World Health Organisation (WHO) classification (all points should be reasonably complied with):

1. **Certain**
   A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definite pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. **Probable/Likely**
   A clinical event, including laboratory test abnormality, with a reasonable time sequence to the administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
3. **Possible**
   A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
4. **Unlikely**
   A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5. **Not related**
   There is sufficient information available to show that the aetiology is unrelated to the IMP.

As an alternative to the options mentioned above, the following assessment can be made:

- The AE is a deterioration of trial disease, which will be analysed as “not related” to IMP.

Challenge: Administration of a suspect product by any route:

- **De-challenge:** Withdrawal of the trial drug from the patient’s therapeutic regimen
  - *Negative* de-challenge: Reaction does not resolve after withdrawal of trial drug without other corrective treatment(s).
  - *Positive* de-challenge: Reaction resolves after withdrawal of trial drug without other corrective treatment(s).
  - Not assessable
- **Re-challenge:** Reintroduction of the trial drug suspected of having caused a reaction following a positive de-challenge
  - *Negative* re-challenge: Reaction does not recur after re-exposure of trial drug, when trial drug was re-administrated under the same conditions.

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- *Positive* re-challenge: Reaction recurs after re-exposure of trial drug, when trial drug was re-administrated under the same conditions.
- Not assessable

Actions taken concerning trial medication will be commented on as follows:

1) None, i.e., IMP was not changed,
2) IMP was interrupted,
3) IMP was withdrawn,
4) Not applicable.

The **course and outcome** of the AE will be commented on as follows:

1) Recovered/resolved,
2) Recovering/resolving,
3) Not recovered/resolved,
4) Recovered/resolved with sequelae,
5) Fatal,
6) Unknown.

Any patient suffering from an AE at trial end has to be followed up until resolution of the AE (recovered without sequelae) or until the AE can be satisfactorily explained (recovered with sequelae). In case the AE is still ongoing, the investigator should issue a final statement concerning the outcome of the AE.

7.2.1.1 Documentation and Reporting of Adverse Events Leading to Withdrawal

In the case of an AE that leads to the withdrawal of an individual subject, the following additional items have to be available from the eCRF as sources for the case narrative in the final integrated clinical trial report:

- Identifiable patient (trial code, year of birth, age, gender, height, weight, race; if relevant, week of pregnancy),
- Noteworthy case history details (e.g., nicotine, alcohol, contraceptives, pacemaker, implants, radiotherapy, physical therapy, diet, allergies, metabolic defects, drug abuse),
- Underlying medical condition and accompanying medical conditions,
- Changes in laboratory parameters in relation to the AE.

7.2.2 Documentation and Reporting of Serious Adverse Events

7.2.2.1 Investigator's Reporting Responsibilities for SAEs

Upon enrolment in the trial, the patients will be instructed to contact the investigator if a serious, unexpected, or AE of special interest occurs during the screening phase, the treatment phase, and during 4 weeks after EOT/WD visit, so that appropriate measures can be taken.

Any SAE (including death, irrespective of the cause) or AESI (whether serious or non-serious) occurring during the screening phase, the double-blind treatment phase, or follow-up phase must be reported by the investigator to the project manager of the CRO and in parallel to the Sponsor's Drug Safety immediately (without undue delay but not later than 24 hours) after it comes to light, irrespective of its relationship with the administration of the IMP (minimum information required: investigator's name/trial site, screening number, visit kit number, date of first dose, date of last dose, date of event, description of event, causality assessment, and countermeasures).

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Coordinating CRO	**proinnovera GmbH** PPD
Sponsor Drug Safety SAE-reporting	**Dr. Falk Pharma GmbH** PPD

A specific SAE reporting form will be provided to the investigators. In case of an SAE or an AESI, this form should be completed, checked, and signed by the investigator as an initial report, and ***sent*** (via fax or scanned e-mail) ***immediately (without undue delay) after coming to light to the trial coordinating CRO and*** the sponsor's Drug Safety in parallel. If required, a follow-up report including all new information obtained on the SAE must be reported using an updated version of the "SAE form" and must be sent again to both parties. SAE information in eCRF should be updated accordingly, when applicable.

The report must contain a detailed description of the symptoms observed and the concomitant treatment administered. Furthermore, the investigator must comment on a possible causative relationship between the SAE and the suspected drug(s) [IMP or concomitant medication]. Each SAE must be followed-up until it is resolved or can be explained satisfactorily.

Every initial report of an SAE is to be verified for completeness and plausibility by the CRO. The date of receipt of the report must be documented by the CRO. If an SAE report is received at the CRO (by fax or scanned e-mail), it is forwarded by the CRO ***immediately*** (with undue delay) after its receipt to the sponsor's Drug Safety in order to verify that respective SAE report has indeed been sent in parallel to both sponsor and CRO. The trial site will be informed promptly of any lacking information or discrepancies by the CRO. ***Follow-up reports will be provided by the investigator each time new information on the SAE becomes available*** (until the case is solved or the patient has recovered). ***For reporting of follow-up information, a similar procedure as for reporting of initial SAEs will apply***.

7.2.2.2 Reporting Responsibilities of the Sponsor

In accordance with drug safety and national requirements, the coordinating CRO's project manager will make sure that, according to national/local requirements, all other involved persons will obtain adequate information.

The general procedure for the observation, collection, and analysis of drug risks (regulatory affairs) in conformity with the appropriate national Drug Law shall apply without qualification.

The sponsor's DSM is responsible for assessing whether an SAR is expected in accordance with the Reference Safety Information (RSI) as provided with the most current version the IB.

For the EU/European Economic Area (EEA) countries and the USA the Sponsor is responsible to report SUSARs electronically to the European Medicines Agency (EMA) (EudraVigilance) and to the Food and Drug Administration (FDA, via an US Agent), respectively. A SUSAR report has to be approved by the Sponsor's Drug Safety Manager before sending it to EudraVigilance and FDA.

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SUSAR reporting to Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and the CAs outside of the European Union will be performed by the CRO according to national/local requirements.

For all countries, the CRO will inform all investigators. The CRO or the investigator (as applicable) will inform the Leading IECs according to national/local requirements, after the report has been reviewed and approved by the sponsor's DSM.

Unblinding of single cases by the sponsor will only be performed if relevant for safety of the trial patient or for notification of a SUSAR (for definition see section 7.1.3.4). Since the definition of every SUSAR requires knowledge of the precise investigational product (or placebo) used, unblinding will be carried out by named staff of the sponsor responsible for drug safety. Only unblinded team members are allowed to look at the individual unblinded SUSAR cases.

The following instructions must be heeded: In the case of an intolerable SAE, the patient must, at the decision of the investigator, be withdrawn from the clinical trial, and symptomatic treatment must be administered. The measures taken must be recorded in the eCRF.

The reporting of AEs and SAEs will be performed according to ICH GCP, CTR (Regulation (EU) No 536/2014) (for EU member states following the transition of the trial), national/local requirements (Non-EU member states) and current Standard Operating Procedures (SOPs) of Dr. Falk Pharma GmbH (or CRO internal SOPs for processes not covered by Sponsor SOPs).

7.3 Abnormal Laboratory Results

The measurements of laboratory values outside of the normal range will be repeated as judged appropriate to ensure the validity of the abnormal result. The investigator will receive laboratory results from the **local laboratory** which **he/she has to enter** on the relevant page of the eCRF. In addition, the investigator will receive laboratory results from the **central laboratory** which **do not need to be entered** on the relevant page of the eCRF, as they are uploaded to the eCRF database. However, the investigator has to assess the aetiology of all abnormal laboratory values on the print-out of the laboratory report as well as in the eCRF. All clinically significant abnormal laboratory values will be followed up until they have normalised, stabilised, or until the trial ends if not resolved earlier.

The investigator has to assess only abnormal laboratory values according to the following ratings:

1 = Not clinically significant,
2 = Clinically significant and causal relationship with trial disease,
3 = Clinically significant and suspected causal relationship with the IMP (i.e., certain, probable/likely, or possible),
4 = Clinically significant and causal relationship with concomitant disease
5 = Clinically significant and causal relationship with concomitant medication,
6 = Technical failure / not done.

If given assessment is "4" or "5" for abnormal laboratory values during the screening phase prior to the first use of IMP, related information has to be provided in the "Medical history and Concomitant Diseases" section of the eCRF.

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In addition, all changes in laboratory values the investigator classifies as clinically significant compared to the baseline must be documented on the AE form of the eCRF.

Causality assessment is compulsory.

7.4 Unblinding by the Investigator in Medical Emergencies

To unblind a patient for identification of treatment allocation IRT system is to be used. Only the investigator is allowed to perform unblinding within the IRT system.

Alternatively, the Drug Safety Department at Dr. Falk Pharma GmbH can be contacted to assist in unblinding a patient. This procedure should only be used in case IRT is not available due to technical issues.

In case of unblinding by the investigator the following must be considered:

- Unblinding should only occur in case of medical emergency, i.e., if it appears necessary for the safety and medical treatment of the patient.
- Whenever possible, prior to unblinding, sponsor should be contacted.
- Premature unblinding is to be documented in the eCRF (reason for unblinding, date).
- Unblinding is to be recorded in the patient's medical records and in the eCRF by reason, date, time, and investigator.

If unblinding is performed via the IRT, the CRO project manager as well as the Sponsor's project manager and DSM will be informed immediately about the unblinding via an automated e-mail.

7.5 Data and Safety Monitoring Board (DSMB) and Independent Data Monitoring Committee (IDMC)

An independent Data and Safety Monitoring Board (DSMB) consisting of two sponsor-independent and trial-independent clinical experts and one sponsor-independent and trial-independent statistician will be established by the sponsor to closely monitor the patients' safety parameters during the trial. This will help the sponsor to react as early as possible to avoid possible risks for the trial participants. The DSMB will have access to blinded data unless or until the DSMB determines that the identities of the treatment groups are necessary for their decision-making. Based on the results of the DSMB meetings, the DSMB will submit its recommendations in written form to the sponsor who is responsible to respond to the recommendations of the DSMB and to take appropriate action if applicable. The DSMB may choose to make additional evaluations at any time if they feel this is justified from the standpoint of safety.

The DSMB will act according to its own written charter and will prepare written minutes of its meetings. The charter of the DSMB will be stored in the Trial Master File (TMF). Specifically, the DSMB will maintain records of its meetings that become part of the Trial Master File when the trial is complete. The frequency of DSMB meetings, parameters to be monitored and further details are described in the DSMB charter.

In order not to disseminate unblinded data and to ensure that all staff involved in the conduct and analysis of the trial remains blinded to the results of the DSMB reviews, only the members of the DSMB including the unblinded statistician (DSMB Chairperson) will have access to these data.

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The DSMB will receive blinded data as further detailed in the DSMB charter for their review. Only in case the DSMB determines that it needs access to unblinded data for their decision, the unblinded statistician will unblind the data by electronically matching the random code of the respective patient(s) requested by the DSMB. He/she will confidentially provide the unblinded data only to the DSMB members.

The members of the DSMB will also constitute the Independent Data Monitoring Committee (IDMC) responsible to conduct and review the efficacy and safety results at the planned IA (see section 9.3.3). In case an IA is performed, only the members of the IDMC will have access to unblinded data. Based on the results of the interim analysis and the underlying decision tree as specified in the IDMC charter, the IDMC will submit its recommendations in written form to the Sponsor who is responsible to respond to the recommendations of the IDMC and to take appropriate action.

Like the DSMB the IDMC (in case that an interim analysis will be conducted) will act according to a written charter and will prepare written minutes of its meetings. The charter of the IDMC determines the members of the IDMC, their responsibility, and data flow. The charter will be stored in the TMF. Specifically, the IDMC will maintain records of its meetings that become part of the TMF when the trial is complete.

In order not to disseminate unblinded data and to ensure that all staff involved in the conduct of the trial remains blind to the results of the IA, only the members of the IDMC and the unblinded staff involved in the statistical analysis will have access to these data.

Before unblinding and in case an IA is performed an interim Statistical Analysis Plan (iSAP), specifying the details regarding the statistical analysis will be prepared and approved by the Sponsor. An SAP for the final analysis will be prepared and approved by the Sponsor before unblinding.

At the optionally planned IA, the randomisation code of the patients to be included in the IA will be unblinded to the IDMC members. The unblinded biostatistician will electronically match the random code of the patients to be included in the IA with the trial data and will send confidentially the results and a brief statistical report summarising the results of the IA to the other IDMC members. The results of the IA will be kept under locked conditions until final unblinding at the end of the trial and then forwarded to the sponsor for TMF filing.

8 CRITERIA FOR PREMATURE TREATMENT DISCONTINUATION AND WITHDRAWAL

8.1 Criteria in Individual Cases

Any patient can prematurely discontinue the treatment with the IMP or withdraw from the trial at any time without personal disadvantages and without having to give a reason. The investigator can also discontinue the treatment after considering the benefit/risk ratio if he/she no longer considers the further treatment justifiable. For patients withdrawn prior to randomisation, a brief reason should be given why the patient is a screening failure (e.g., violation of in-/exclusion criteria (to be specified), patient's request to withdraw). For all randomised patients who are prematurely discontinued from the treatment with the IMP or who are prematurely withdrawn from the trial, the date of premature discontinuation from treatment or withdrawal and the primary reason for the premature discontinuation of treatment or withdrawal, as well as the observations available at the time of premature discontinuation of treatment or withdrawal are to be documented in the eCRF. Reasons

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leading to the premature discontinuation of treatment or withdrawal from trial of a randomised patient can include the following (**only <u>one</u> primary reason must be determined**):

- **Lack of clinical efficacy**, e.g.:
  - Progress of trial disease defined as not bearable clinical symptoms compared to baseline (over 2 subsequent weeks)
- **Intolerable AE** (to be specified), which precludes, in the opinion of the investigator, further treatment with the IMP or further trial participation of a patient.
- In case of a clinically significant QTcF-prolongation during the course of the trial, the investigator in consultation with the DSM of the sponsor and the responsible MM has to decide whether the patient should continue with the IMP treatment or not. In case of **QTcF prolongation of > 500 msec** or **QTcF increase of 60 ms** compared to baseline level, IMP has to be discontinued. In case of occurrence of **Serotonin Syndrome** defined according to Hunter Serotonin Toxicity Criteria, IMP has to be discontinued (see also section 7.1.2).
- In case of suspected **Drug-Induced Liver Injury (DILI)** as defined below
  - ALT or AST > 8 x ULN or
  - ALT or AST > 5 x ULN for more than 2 weeks or
  - ALT or AST > 3 x ULN and (TBL > 2 x ULN or INR > 1.5) or
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) treatment with the IMP has to be discontinued.
- In case of a confirmed myocardial infarct or stroke, IMP has to be discontinued (see also section 7.1.2).
- In case of severe diarrhea associated with volume depletion, IMP has to be discontinued (see also section 7.1.2).
- In case of clinical worsening of depression and emergence of suicidal thoughts and behavior, IMP has to be discontinued (see also section 7.1.2).
- **Lack of patient's cooperation**, e.g.:
  - Patient's request to withdraw,
  - Lack of compliance or patient fails to attend the interim visits as agreed,
  - Technical/logistical reasons (e.g., a change in place of residence, not referred by family physician, etc.),
- **Pregnancy** – In case a patient becomes pregnant during the trial, the patient has to discontinue the IMP treatment immediately. Details on pregnancy tests are outlined in section 6.4.5, reporting requirements are outlined in section 7.1.4.
- **Other reasons** (to be specified), e.g., did not meet in-/exclusion criteria (coming to light after randomisation) and which would place the patient, in the opinion of the Sponsor or the investigator on risk for further trial participation.

In all randomised patients who finish the treatment phase prematurely, a withdrawal examination must be carried out within 48 hours after the last intake of the IMP. The withdrawal examination must be conducted as an EOT examination and documented in the eCRF. Whenever possible, the assessment for the efficacy variables should be performed, i.e., it is most important to evaluate the ANMS GCSI-DD.

If possible, a FU visit (V7) four weeks after the WD visit (V6) should be performed in addition for safety reasons.

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The investigator will continue to observe patients withdrawn from the trial because of intolerable AEs until the findings have been clarified.

In general, withdrawn patients will not be replaced.

8.2 Criteria for the Termination of the Trial

The Sponsor may decide to temporarily halt the trial, to terminate the whole trial, parts of the trial or to discontinue an individual investigational site at any time.

Of note: After transition of the trial, EU member states should follow general rules for temporary halt, premature termination or suspension of the trial defined by CTR (Regulation (EU) No. 536/2014; in particular *Articles 37* and *38*).

8.2.1 Termination of the Whole Trial

Reasons for study termination may include, but are not restricted to:

- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug,
- A Competent Authority (CA) demands that the study be terminated,
- Withdrawal of Independent Ethics Committee's (IEC's)/Institutional Review Board's (IRB's) approval of the study,
- Unsatisfactory enrolment of subjects, that cannot be expedited by appropriate measures,
- Critical issues related to quality or quantity of data,
- If systematic severe violations of GCP, the trial protocol and misconduct occur which unacceptably affect the safety or rights of the patients or render questionable the validity of the overall trial results.

Moreover, if an unexpected, serious, or unacceptable risk to subjects enrolled in the study is discovered, the Sponsor must terminate or interrupt (temporary halt) the trial, especially in the following cases:

- If ADRs occur with a frequency or intensity which significantly differ from the data reported in the IB and which lead to a negative risk-benefit ratio,
- If a serious ADR with the same reaction term (preferred term [PT]) occurs in more than 5% of the planned study population, i.e., in more than 16 patients,
- If the results of parallel clinical trials with the same IMP show evidence for unacceptable risks.

Details on the possibility to stop the trial based on results of the interim analysis (planned to be conducted optionally) are described in section 9.3.3.

8.2.2 Termination of the Trial at an Investigational Site

Conditions that may warrant termination of a study site include, but are not limited to:

- Failure of the Investigator to comply with GCP guidelines,
- Submission of knowingly false information from the research facility to the Sponsor, Study Personnel, or Regulatory Authorities,
- Insufficient adherence to protocol requirements,

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- An investigational site can be closed unless it has recruited at least 2 patients within 4 months after initiation.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Efficacy and Safety Variables and Endpoints

9.1.1 Primary Efficacy Endpoint

- Change of the ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT/WD (V6).

  The daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) divided by 5.

9.1.2 Secondary Efficacy Endpoints

- Change of the modified ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT/WD (V6).

  The modified daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) plus the score value for bloating divided by 6.
- Change of the composite ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT/WD (V6)

  The composite daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of only 4 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain) divided by 4.
- Change of the ANMS GCSI-DD average weekly symptom score for *nausea* from BSL (V2) to EOT/WD (V6).
- Change of the ANMS GCSI-DD average weekly symptom score for *early satiety* from BSL (V2) to EOT/WD (V6).
- Change of the ANMS GCSI-DD average weekly symptom score for *postprandial fullness* from BSL (V2) to EOT/WD (V6).
- Change of the ANMS GCSI-DD average weekly symptom score for *upper abdominal pain* from BSL (V2) to EOT/WD (V6).
- Change of the ANMS GCSI-DD average weekly symptom score for *number of vomiting episodes* from BSL (V2) to EOT/WD (V6).
- Change of the ANMS GCSI-DD average weekly symptom score for *bloating* from BSL (V2) to EOT/WD (V6).
- Change of the ANMS GCSI-DD average weekly item score *overall severity of gastroparesis symptoms* from BSL (V2) to EOT/WD (V6).
- Change of the PAGI-SYM total score from BSL (V2) to EOT/WD (V6).
- Change of the GCSI total score from BSL (V2) to EOT/WD (V6).
- Change in gastric emptying $T_{1/2}$ measured by GEBT from BSL (V2) to EOT/WD (V6).

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9.1.3 Exploratory Endpoints

Treatment phase

- Change of the ANMS GCSI-DD average weekly total symptom score from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Area under the curve (AUC) of the ANMS GCSI-DD total symptom score from day 1 (BSL, V2) to day 85 (EOT, V6).
- Change of the modified ANMS GCSI-DD average weekly total symptom score from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Change of the ANMS GCSI-DD average weekly symptom score for *nausea* from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Change of the ANMS GCSI-DD average weekly symptom score for *early satiety* from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Change of the ANMS GCSI-DD average weekly symptom score for *postprandial fullness* from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Change of the ANMS GCSI-DD average weekly symptom score for *upper abdominal pain* from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Change of the ANMS GCSI-DD average weekly symptom score for *number of vomiting episodes* from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Change of the ANMS GCSI-DD average weekly symptom score for *bloating* from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Change of the ANMS GCSI-DD average weekly item score *overall severity of gastroparesis symptoms* from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78.
- Treatment response 1 (yes, no), defined as a decrease of the ANMS GCSI-DD average weekly total symptom score by ≥0.5 points from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 and to EOT/WD (V6).
- Treatment response 2 (yes, no), defined as a decrease of the ANMS GCSI-DD total score by ≥30% from BSL (V2) to Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 and to EOT/WD (V6).
- Time (in days) to treatment response 1 (yes, no), defined as a decrease of the ANMS GCSI-DD average weekly total symptom score by ≥0.5 points from BSL (V2).
- Time (in days) to treatment response 2 (yes, no), defined as a decrease of the ANMS GCSI-DD total score by ≥30% from BSL (V2).
- Change of PAGI-SYM total score from BSL (V2) to Day 15, 29, 57 and to EOT/WD (V6).
- Change of GCSI total score from BSL (V2) to Day 15, 29 57 and to EOT/WD (V6).
- Change of PAGI-QoL from BSL (V2) to EOT/WD (V6).
- Change of PGI-S score from BSL (V2) to Day 15, 29, 57 and to EOT/WD (V6).
- PGI-C score at Day 15, 29, 57 and at EOT/WD (V6).
- Change of EQ-5D-5L from BSL (V2) to EOT/WD (V6).
- Change of the CGI-S from BSL (V2) to Day 15, 29, 57 and to EOT/WD (V6).
- CGI-C score at Day 15, 29, 57 and at EOT/WD (V6).
- Number of days with intake of rescue medication from BSL (V2) until EOT/WD (V6).

Follow-up phase

- Change of the ANMS GCSI-DD total score from EOT/WD (V6) to end of 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).

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- Change of the modified ANMS GCSI-DD total score from EOT/WD (V6) to 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).
- Change of the ANMS GCSI-DD symptom score for *nausea* from EOT/WD (V6) to 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).
- Change of the ANMS GCSI-DD symptom score for *early satiety* from EOT/WD (V6) to 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).
- Change of the ANMS GCSI-DD symptom score for *postprandial fullness* from EOT/WD (V6) to 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).
- Change of the ANMS GCSI-DD symptom score for *upper abdominal pain* from EOT/WD (V6) to 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).
- Change of the ANMS GCSI-DD symptom score for *number of vomiting episodes* from EOT/WD (V6) to 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).
- Change of the ANMS GCSI-DD symptom score for *bloating* from EOT/WD (V6) to 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).
- Change of the ANMS GCSI-DD item score *overall severity of gastroparesis symptoms* from EOT/WD (V6) to 1st, 2nd, 3rd treatment-free week and to FU/EOS (V7).
- Change of PAGI-SYM total score from EOT/WD (V6) to FU/EOS (V7).
- Change of GCSI total score from EOT/WD (V6) to FU/EOS (V7).
- Change of PGI-S score from EOT/WD (V6) to FU/EOS (V7).
- Change of EQ-5D-5L from EOT/WD (V6) to FU/EOS (V7).
- Change of the CGI-S from EOT/WD (V6) to FU/EOS (V7).

9.1.4 Safety Variables

- Adverse Events (AEs)
- Vital signs (blood pressure, heart rate) and body weight
- 12-lead ECG
- Haematology, blood chemistry, urinalysis
- Assessment of tolerability by investigator and participant

9.2 Statistical Analysis Sets

The following analysis populations will be defined for the evaluation.

9.2.1 All Patients Screened

The set of all patients screened will include all patients with data documented at SCR 1 (V0).

9.2.2 Safety Analysis Set

The safety analysis set will include all randomised patients (as treated) who received at least one dose of IMP. If the administration of any IMP is not certain, the patient will be included in the safety set.

9.2.3 Full Analysis Set

The full analysis set (FAS), defined according to the intention-to-treat (ITT) principle, will include all randomised patients (as randomised) who received at least one dose of IMP. The ITT principle will be preserved despite the exclusion of patients who took no IMP, as the

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decision of whether or not to begin treatment is not influenced by knowledge of the assigned treatment.

9.2.4 Completer Set

The completer set will include all patients from the FAS (as randomised) who attend the scheduled EOT visit (V6) and provide evaluable diary records for the primary endpoint.

9.2.5 Per-protocol Set

The patients within the per-protocol set (PPS) consists of all subjects from the FAS and who should especially fulfil the following criteria:

- All of the major inclusion criteria, none of the major exclusion criteria fulfilled,
- Absence of major protocol deviations during the DB treatment phase,
- Correct allocation to treatment group,
- Sufficient compliance concerning administration of IMP (at least 80% of IMP) during the DB treatment phase,
- No premature discontinuation from the DB treatment phase, unless this was due to lack of efficacy, or due to an ADR, or due to an intolerable adverse event which is a deterioration of trial disease,
- Evaluable primary efficacy variable at least at BSL (V2) and EOT (V6).

The classification of major and minor protocol deviations and major and minor in- and exclusion criteria as well as the resulting definition of analysis sets will be performed prior to unblinding and will be approved by the sponsor. A summary of the number of patients per analysis set will be given and reasons for exclusion of a patient from an analysis set will be listed.

9.3 Statistical Evaluation

The primary objective of the trial is to compare the efficacy of different doses of naronapride vs. placebo over 12 weeks on disease signs and symptoms in patients with at least moderate symptoms of idiopathic or diabetic gastroparesis.

Three verum groups (groups A, B, and C) with increasing daily dose strength will be compared with placebo (group D), respectively:

Group A: Naronapride low daily dose (10 mg TID)

Group B: Naronapride medium daily dose (20 mg TID)

Group C: Naronapride high daily dose (40 mg TID)

Group D: Placebo (TID)

The primary efficacy variable will be subjected to a confirmatory statistical analysis ($\alpha = 0.025$, one-sided testing) for the three verum groups versus placebo. Evaluations of secondary efficacy and safety variables will be understood in the exploratory sense. Besides tables containing statistical results, accompanying figures will be created where appropriate.

Details of the statistical analysis will be described in a separate statistical analysis plan.

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9.3.1 Evaluation of the Primary Efficacy Endpoint

9.3.1.1 General Approach

The primary efficacy endpoint will be subjected to a confirmatory statistical analysis ($\alpha = 0.025$, one-sided) for the three test groups in the context of a multi-arm, two-stage, group-sequential adaptive trial design[33] for testing in many-to-one comparisons as described in section 9.3.3. One optional interim analysis is planned, which will only be conducted, if warranted by actual recruitment status. For the final analysis, all patients qualifying for the different analysis sets will be included in the analysis. The evaluation of the primary efficacy endpoint at interim analysis (if applicable) will be performed according to the primary estimand.

Confirmatory testing will be performed according to the following hypotheses:

Null hypothesis	Alternative hypothesis
$H_{01}: \mu_A - \mu_D \geq 0$	$H_{11}: \mu_A - \mu_D < 0$
$H_{02}: \mu_B - \mu_D \geq 0$	$H_{12}: \mu_B - \mu_D < 0$
$H_{03}: \mu_C - \mu_D \geq 0$	$H_{13}: \mu_C - \mu_D < 0$

μ_A, μ_B, μ_C and μ_D denote the change of the ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT (V6) in the naronapride 10 mg TID group (A), naronapride 20 mg TID group (B), naronapride 40 mg TID group (C) and the placebo group (D).

To date, it is not clear which of the three dose strengths (10, 20 or 40 mg TID) will be more efficacious and therefore no a-priori ordering of hypotheses is possible. The null hypotheses will be tested using the Dunnett procedure, which preserves the familywise α-level in this many-to-one comparison. If an interim analysis is performed, the efficacy for at least one treatment arm will be proven after the interim analysis if the respective test statistic resulting from the inverse normal method exceeds the critical value determined by the O'Brien-Fleming α-spending function.

If at least one null hypothesis cannot be rejected, the trial may be continued with the originally planned sample size or with a recalculated sample size based on the effect size estimation of the interim analysis.

The null hypotheses will be tested using the closure principle with Dunnett's procedure and the inverse normal method for combining the p-values for a second time at the final analysis. The critical value at the final analysis will be determined by the O'Brien-Fleming α-spending function. This procedure preserves the overall (experiment-wise) type I error rate of $\alpha = 0.025$ in a strong sense. For a detailed description of rejection rules at interim and final analysis refer to section 9.3.3.

The difference between each treatment group and placebo in the mean change of the ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT/WD (V6) will be calculated and the corresponding two-sided 95% repeated confidence intervals (RCI) will be provided.

The following subgroups will be considered for exploratory analyses:

- Gender (male, female, divers)
- Age in groups
- Type of gastroparesis (idiopathic, diabetic)
- Severity of gastroparesis (moderate, severe, or very severe)

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- Duration of disease (<5 years, ≥5 years)

Further subgroups might be defined in the statistical analysis plan.

9.3.1.2 Definition of Estimands

In this trial the estimands will be constructed according to the primary objective "to evaluate the efficacy of a 12-week treatment with naronapride compared to placebo on disease signs and symptoms in participants with at least moderate idiopathic or diabetic gastroparesis" (see section 2).

The treatment regimen under evaluation is an anticipated 12-weeks treatment interval with the randomised IMP taken TID without administration of any concomitant medication that possibly influences the efficacy assessments.

For the evaluation of the primary objective of the trial, five different estimands will be defined: a primary and 4 secondary estimands.

All five estimands will use the patient level weekly average of the ANMS GCSI-DD total symptom score as subject level endpoint.

The population level summary will be the mean change from BSL (V2) of the ANMS GCSI-DD total symptom score at the EOT/WD visit (V6) between the treatment groups.

Primary estimand

The primary estimand will be a treatment policy estimand using all patients within the FAS and all observed values for the evaluation regardless of the occurrence of an intercurrent event (ICE). Consequently, the only ICE, which handling has to be specified is premature termination (independent of the reason for termination).

The primary estimator will be an adequate contrast of a mixed model repeated measure procedure (MMRM). The model will include the fixed factors treatment group, time, treatment-by-time interaction, and type of gastroparesis (idiopathic, diabetic) and time as repeated effect. A secondary estimator will be similar to the primary estimator but implementing a multiple imputation-based strategy within the treatment group. A third estimator will be the subjects-based change from BSL, V2 (i.e., using the raw differences) applying a last observation carried forward (LOCF) imputation.

Secondary estimand I

The first secondary estimand will be a hypothetical estimand, that is we assume a hypothetical population where the ICE premature termination would have not occurred regardless of the occurrence of other ICEs.

The main estimator will be derived from an analysis of covariance (ANCOVA) model using the fixed factors treatment group, type of gastroparesis, and Baseline ANMS GCSI-DD average weekly total symptom score as covariate. A secondary estimator will be similar to the primary estimator but using all time points in the model. This estimator will use the mean of the subject level changes from BSL, V2 (raw differences).

Secondary estimand II

The second secondary estimands will be a while-on-treatment estimand comparing the groups while the subjects took the IMP. The relevant ICE is the premature discontinuation of medication regardless of the reason of discontinuation and other ICEs.

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The main estimator will be derived from an MMRM while missing values will be imputed by LOCF. A secondary estimator will use the MMRM model without explicit imputation as described for the primary estimator of the primary estimand.

Secondary estimand III

The third secondary estimand will be a without-rescue-medication estimand comparing the groups while the subjects took the IMP without using rescue medication for more than 2 days per week. The relevant ICE is the use of rescue medication on more than 2 days per week regardless of other ICEs.

The main estimator will be derived from an MMRM while missing values will be imputed by LOCF. A secondary estimator will use the MMRM model without explicit imputation as described for the primary estimator of the primary estimand.

Secondary estimand IV

The fourth secondary estimand will be again a hypothetical estimand comparing the treatment groups in a hypothetical population where no major protocol deviations or relevant ICE would appear that is, it will be a population as described for the PPS.

The estimator of this estimand will be the same as the primary estimator of the primary estimand.

9.3.2 Evaluation of the Secondary Efficacy Endpoints and Exploratory Endpoints

The evaluation of secondary efficacy and exploratory endpoints will be performed for the full analysis set (ITT analysis).

Continuous variables will be summarised using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Categorical data will be described using absolute and relative frequencies. Where proportions of patients are analysed, the denominator will be the number of patients for which the variable can be assessed. In the very unlikely case of a high proportion of patients with no valid value, robustness analyses may be considered. Shift tables will be provided where appropriate. AUC will be computed using the trapezoidal rule. Time to event analysis will utilize the Kaplan-Meier estimator and appropriate statistical tests. The analysis will be described in more detail in an SAP.

All p-values resulting from statistical tests will be interpreted in an exploratory sense. Supportive and sensitivity analyses will be performed after the final analysis or, if the trial was stopped prematurely, after the interim analysis (if applicable).

9.3.3 Interim Analysis

Optionally the trial will include an interim analysis (IA).

The IA is planned to be carried out when the first 192 consecutively randomized FAS-patients have reached their primary endpoint at EOT/WD (V6) (60% of the overall planned number of patients, information rate: 0.60), but only if warranted by the actual recruitment status. Recruitment will be monitored in a blinded fashion and the decision on performing the interim analysis will solely be made on blinded information at the time of randomization of the last patient scheduled for the interim analysis.

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The decision on whether or not to conduct an IA will be made by the sponsor upon randomization of the last patient scheduled for IA.

Based on the calculated timelines for the conduct of the IA and based on the recruitment progress within the last 3 months, an IA will only be conducted if the results from the IA can be obtained at least 4 weeks prior to the projected inclusion of the last patient (LPI = 320).

In case an optional IA will be performed, the trial will be conducted according to a 2-stage group sequential adaptive test design with O'Brien and Fleming shaped boundaries with possible sample size adaptation and treatment arm selection after the interim analysis.

The interim analysis aims at:

1. Verifying the assumptions of the sample size calculation and continuation of the trial as planned or recalculating sample size based on the effect size estimations of the interim analysis and based on conditional power assessments.
2. Investigating which active treatment arm, if applicable, should be stopped after the interim analysis.
3. Early stopping of the trial for efficacy or futility or safety. There will be no binding stopping rule for futility.

Planning a possible interim analysis is justified according to the 'Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design' (CHMP/EWP/2459/02)[34] because current knowledge on the effect size of the treatment groups is limited.

As described for the final analysis in section 9.3.1, the null hypotheses specified in section 9.3.1 will be tested in a confirmatory sense against the alternative hypotheses for the interim and final analysis using the procedure of Dunnett.

Recruitment of patients will be continued during the performance of the interim analysis.

Rejection of a null hypothesis will be possible at the interim analysis if the p-values with respect to the null hypothesis and all logically related hypotheses fall below α_1, where α_1 is determined by the O'Brien-Fleming α-spending function. The corresponding overall values are shown in the following table.

Stage	Information Rate	Critical value	Significance level (one-sided)	Alpha spent
1	0,6	2,572	0,0051	0,0051
2	1	1.992	0,0232	0,0250

The displayed critical value is on the z-value scale (calculated from the spent alpha levels). The critical value after the first part derived from the global Dunnett test with 3 active groups and with the corresponding α-level of 0.0051 (degrees of freedom [df]=188, correlation=0.5 due to the equal groups sizes) is 2.945.

A null hypothesis will be rejected at the final stage if the values of the respective inverse normal combination functions belonging to the null and all logically related hypotheses exceed the critical value on the z-scale.

If being conducted, the interim analysis will be performed by an unblinded biostatistician, and the results and a short statistical report will be provided to an IDMC. The

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recommendations of the IDMC may include stopping the whole trial or treatment arms for early efficacy if the inverse normal test statistic(s) exceed(s) the critical value determined by the O'Brien-Fleming α-spending function and actual information fraction. The IDMC may also consider a recommendation towards continuing the trial in spite of the test statistic(s) exceeding the critical value if they believe that further substantiation of the positive result is needed. Similarly, the IDMC can recommend stopping the whole trial or treatment arms for futility or due to efficacy at the interim analysis.

The occurrence of treatment-emergent AEs and ADRs – based on their distribution to treatment groups and severity – may also lead to the stop of the entire trial at the discretion of the sponsor.

In case a null hypothesis will be rejected at the interim analysis and the trial recruitment for a treatment arm or the whole trial will be stopped thereafter, the interim analysis is considered as the primary confirmatory analysis. A robustness analysis will additionally be performed also including the overrunning patients.

Further details regarding the interim analysis will be described in the respective SAP for the interim analysis (iSAP).

9.3.4 Influence of Centre and Covariates

Possible country (or geographical cluster) and centre effects will be evaluated on an exploratory level by tabulation of the primary efficacy variable by country (or geographical cluster) and centre, respectively. Any pooling of centres or countries with few patients in geographical clusters will be specified in the statistical analysis plan before breaking the blind.

Furthermore, the primary efficacy endpoint will be analysed descriptively with respect to the subgroups specified in section 9.3.1.1.

9.3.5 Exploring Clinically Meaningful Within-Patient Changes in Sign and Symptom Scores

The 2019 FDA draft guidance on gastroparesis clinical trials and endpoints[17] provides emphasis on clinically significant within-patient changes with PROs to define possible responder thresholds for further phase III clinical trials.

As proposed in this guidance, an anchor-based approach will be applied to estimate clinically meaningful changes, using PGI-S and PGI-C as anchors.

Further details will be given in an SAP.

9.3.6 Safety Analysis

The safety evaluations will include analyses of AEs, vital signs and body weight, laboratory measurements, ECG (12-lead), and assessment of tolerability by investigator and patient. The analysis of safety will be based on the safety set.

AEs

Pre-treatment AEs of non-randomised subjects will only be listed. This listing is based on all subjects screened and not randomised.

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Pre-treatment AEs (of randomised patients), TEAEs and post-treatment AEs will be analysed separately. In addition, TEAEs and post-treatment AEs will be evaluated together.

The incidence of TEAEs and post-treatment AEs will be summarised for each treatment group by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and PT. If a patient reports the same AE more than once, then this patient will only be counted once with respect to the corresponding SOC / PT code, using the most severe intensity.

An overview of the absolute and relative frequencies of patients with at least one AE will be given for the categories "pre-treatment", "treatment-emergent", "post-treatment" and "treatment-emergent or post-treatment" by seriousness, severity, causality, measures, and outcome.

The following analyses will be performed for TEAEs:
- Tables will present the absolute and relative frequencies of patients with at least one TEAE classified by SOC and PT.
- The absolute and relative frequencies of patients with a drug related TEAE will be summarised by SOC and PT
- The absolute and relative frequencies of patients with at least one treatment-emergent SAE will be summarised by SOC and PT
- The absolute and relative frequencies of patients with TEAEs leading to premature discontinuation will be summarised by SOC and PT

The following analyses will be performed for TEAEs and post-treatment AEs together:
- Tables will present the absolute and relative frequencies of patients with at least one AE classified by SOC and PT.
- The absolute and relative frequencies of patients with at least one SAE will be summarised by SOC and PT.

Individual patient data listings will be provided for all deaths, patients with other SAEs, unexpected adverse drug reactions (as confirmed by the sponsor's DSM), discontinuation of IMP due to AEs, or premature trial termination due to AEs.

Laboratory measurements

Laboratory data will be subjected to both a quantitative analysis (descriptive summary statistics) and qualitative analysis where frequencies of normal, above normal, and below normal values will be computed.

The following analyses will be performed:
- Standard descriptive summary statistics will be calculated at each scheduled measuring time point and the last individual measuring time point.
- Standard descriptive summary statistics will be calculated for the absolute change from BSL (V2) to each scheduled visit up the last individual time point.
- Frequencies of normal, above normal, and below normal values will be computed at each scheduled measuring time point and the last individual measuring time point.
- Shift tables displaying changes with respect to the normal range from BSL (V2) to each scheduled visit up to the last individual time point will be provided.
- A listing of all patients with abnormal (above normal or below normal) values at any time point will be given

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Findings from ECG (12-lead)

Frequencies for the respective categories of (ab)normality will be tabulated.

Assessment of tolerability by investigator/patient

The investigators and patients' assessment of tolerability of the trial medication at EOT/WD (V6) will be analysed by frequencies in the pre-specified categories CCI [redacted]

9.3.7 Exposure to Trial Drug and Compliance

Exposure to trial drug will be summarised using descriptive statistics for the number of naronapride (or placebo) tablets distributed to the patient and the calculated number of tablets taken by the patient.

Patient's compliance with respect to the administration of the IMP will be calculated as the ratio between actually applied medication (as determined from the amount dispensed minus the amount documented by the investigator as returned after counting of returned IMP) and the amount of medication theoretically required to be applied in the individual interval of treatment.

Patients with a ratio of at least 80% will be considered as sufficiently compliant.

9.3.8 Missing Values

Generally, missing values of the efficacy and safety laboratory parameters will not be imputed. One major exception is the primary endpoint, where the imputation strategies are described in the section on the estimands. Secondary efficacy endpoints will generally be analysed by likelihood-based methods resulting in consistent estimates under the missing at random (MAR) assumption.

The daily ANMS GCSI-DD total score is the sum of the scores (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) divided by 5. If at least one symptom score is missing for a day, the ANMS GCSI-DD total score is regarded as missing for this day.

In accordance with the original planning and in accordance with the calculation as provided in the eCRF (for details refer to section 6.4.12.1), the daily ANMS GCSI-DD total score will also be calculated if only 4 of the 5 core symptoms has been assessed on the respective day. In this case the ANMS GCSI-DD total score will be the sum of remaining 4 core symptom items divided by 4. Such an analysis of the weekly average score of the ANMS GCSI DD based on this calculation will be performed as a sensitivity analysis.

The ANMS GCSI-DD total symptom score for a week is the average of the daily total scores over the 7 days of a week regardless the use of rescue medication.

In case of 1 or 2 missing daily total scores the ANMS GCSI-DD total score within a week, the mean will be calculated based on the 5 or 6 available values, respectively. If data of less than 5 days are available (> 2 days missing) the ANMS GCSI-DD total score will not be evaluable for the respective week.

For the purpose of another sensitivity analysis the following rule will be applied: In case that rescue medication (preferably dimenhydrinate, alternatively cyclizine or meclozine) has been taken on a given day, the score values for the ANMS GCSI-DD will be set to missing

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for this day and the rule for missing values will be applied for the weekly average. If the documentation of the intake of dimenhydrinate (or cyclizine or meclozine) is missing, then no intake will be assumed.

No imputation methods for other missing values are planned to be performed.

9.3.9 Miscellaneous

Only the primary result of the primary efficacy endpoint will be interpreted in a confirmatory sense. All other analyses performed on the primary efficacy endpoint (subgroup analyses), on secondary efficacy endpoint, exploratory endpoints and on safety variables have purely explorative character. An adjustment of α (type I error) is therefore not necessary for these kinds of analyses.

A more detailed SAP will be prepared before unblinding and approved by the sponsor. In the SAP, the trial data sets will be defined, and all details of the principal features stated in the protocol will be described.

The statistical analysis will be performed using the software package SAS version 9.4 or higher (SAS Institute Inc., Cary, NC 27513, USA) or comparable software if applicable. Results reported in the context of the adaptive design will be calculated using the statistical software package R (Version 4.0.4, https://www.R-project.org) and the package R-PACT; R Package for Adaptive Clinical Trials (Version 3.0.4) or higher.

All individual data as well as results of statistical analyses – whether explicitly discussed in the previous sections or not – will be presented in individual patient data listings and statistical summary tables. Descriptive statistics and frequencies of categories will usually be calculated for each treatment group separately.

In general, continuous variables will be summarised using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Categorical data will be described using absolute and relative frequencies. Shift tables will be provided, where appropriate. The absolute change from BSL (V2) to a visit will be calculated as the value at the visit minus the baseline value. Relative changes (%) are calculated by dividing the absolute change by the baseline value and multiplication with 100 to obtain a percentage, where appropriate. Any changes in the planned statistical methods will be documented in the clinical study report (CSR).

The following international dictionaries will be used for medical coding:

- Diagnoses: MedDRA
- Medications: WHO Drug Global including ATC (Anatomical Therapeutical Chemical) classification
- Adverse events: MedDRA

9.4 Sample Size Calculation

The primary objective of the trial is to compare the efficacy of different doses of naronapride vs. placebo over 12 weeks on disease signs and symptoms in patients with at least moderate symptoms of idiopathic or diabetic gastroparesis.

The primary efficacy endpoint in this clinical trial is the change of the ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT/WD (V6).

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The overall α-level is set to 0.025 (one-sided). The statistical hypotheses for the primary efficacy endpoint will be analysed following applying the closure principle with the procedure of Dunnett within the adaptive design.

The trial has been planned according to a 2-stage multi-arm group-sequential adaptive design with the option of sample size adjustment, stopping of treatment arms, or early stopping of the trial for efficacy, futility, or safety after the planned interim analysis. There are no binding stopping rules for futility boundaries. If warranted by the actual recruitment status, the interim analysis is planned to be performed after 60% of the planned number of randomised patients have completed the trial (information rates: 0.6, 1.0).

According to the user manual for the ANMS GCSI-DD, the minimum clinically important difference in the ANMS GCSI-DD score has been estimated to be 0.50(35). The standard deviation is set to 1.22 and exceeds the highest reported standard deviation in clinical trials of gastroparesis.[36]

A power of 80%, where power is defined as rejection of at least one null hypothesis, as target to detect the assumed treatment effect yields a sample size of 80 patients per treatment group. Therefore, the planned sample size is 320 patients (1:1:1:1 randomisation) in the FAS. Assuming a screening failure rate of a maximum of 50 to 60%, it is assumed that 640 to 800 patients need to be screened for this trial.

The critical values of the group sequential test design were calculated for the standardized (cumulative) test statistic for the O'Brien-Fleming type design. The critical values at the interim and final analysis will be determined by the O'Brien-Fleming α-spending function and actual information fraction as further detailed in an SAP.

Sample size calculation was performed using the statistical software package R (Version 4.0.4, https://www.R-project.org) and the package R-PACT; R Package for Adaptive Clinical Trials (Version 3.0.4).

9.5 Data Management

Almost all patient data collected during the trial will be captured using an eCRF. Patient questionnaires and patient's diaries (PROs), which will be in local language will also be provided electronically (ePROM), except the QD-5D-5L. The QD-5D-5L questionnaire will be provided as a paper-based version in local language and results from this questionnaire need to be transferred to the eCRF by study staff. These documents are considered part of the eCRF. Also results from central laboratory assessments will be made available in the eCRF. Detailed results from the GEBTs (except $t_{1/2}$) as far as not necessary for the conduct of the trial on site, will be transferred to the Data Management electronically by the GEBT provider and will finally be added to the clinical database. Details on the transfer of external data (e.g., upload of central laboratory data) will be specified in a Data Transmission Agreement (DTA).

The overall procedures for quality assurance of clinical trial data are described in the respective SOPs of the CRO. In addition, CRO will prepare a Data Management Plan (DMP) to describe the procedures and processes of e.g., eCRF implementation, data collection and data coding. All plausibility checks will be defined in the Data Cleaning Plan (DCP) to be approved by the Sponsor.

Systematic data validation will be performed through the discrepancy management system within the eCRF (e.g., check of ranges, consistency, and plausibility). This includes online

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checks as well as offline checks, used to check more complex relation of data. These will be reviewed by qualified data management and medically qualified personnel for completeness, consistency, and plausibility. Unclear data will be clarified using queries. Procedures of data entry and data cleaning will be tracked and appropriately documented in the audit trail of the eCRF.

9.6 Randomisation and Blinding

In the double-blind treatment phase, patients eligible for this trial will be centrally randomised based on a computer-generated randomisation list and assigned in a 1:1:1:1 ratio to one of the four treatment arms of the double-blind treatment phase (group A: Naronapride 10 mg TID, group B: Naronapride 20 mg TID, group C: Naronapride 40 mg TID and group D: placebo). Randomisation will be performed at BSL (V2) using IRT.

Randomisation will be stratified by type of gastroparesis (idiopathic, diabetic) in a 2:1 ratio. This stratification ensures balanced allocation of trial participants to treatment groups within the type of gastroparesis.

To ensure a better balance compared to simple randomisation, randomisation will be performed using randomly permuted blocks within strata.

For details on visit kit allocation during the treatment phase refer to section 3.1 and section 5.3.

Randomisation data will be kept strictly confidential, accessible only to authorised persons as mentioned below and as not otherwise involved in the conduct of the trial, until the time of unblinding.

Two hardcopies of the randomisation list will be prepared and sealed by staff of CRO who is not involved in the trial conduct. One sealed list will be used by the Sponsor's quality control manager responsible for production and packaging of the IMPs, one will be used by the company performing packaging of the IMPs, where the randomisation list will not be accessible to others than production staff.

The responsible Drug Safety Manager at the Sponsor's Drug Safety Department will receive emergency envelopes to ensure the blinding.

Investigators will be able to unblind patient's treatment through the IRT. Alternatively, the Drug Safety Department at Dr. Falk Pharma GmbH can be contacted to assist in unblinding a patient. This procedure should only be used in case IRT is not available due to technical issues (see section 7.4). Unblinding by investigator must happen only in an emergency case when information about the patient's medication is required in order to determine further treatment of the patient.

Unblinding of single cases will also be performed before notification of a SUSAR (for definition see section 7.1.3.4). Since the definition of a SUSAR requires knowledge of the investigational product (or placebo) used, unblinding will be carried out by named staff of the sponsor responsible for drug safety. Only two members of the Sponsor's Drug Safety Department are allowed to look at the individual unblinded SUSAR cases.

The following procedure will be applied for unblinding prior to the interim and final statistical analysis: The responsible statistician gives a written confirmation that all unblinding requirements are fulfilled, e.g., database closure, which will be followed by a written instruction of the sponsor's trial manager for unblinding.

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10 PROTOCOL AMENDMENT(S)

Protocol amendments that become necessary during the course of the clinical trial will become a formal part of the protocol in the form of an amendment, by agreement between Dr. Falk Pharma GmbH (responsible project manager), the CRO (responsible project manager and statistician), the Trial Coordinating Investigator (TCI) and the Country Coordinating Investigator (CCI). Amendments must be signed by all of these parties. The CRO who will take over the overall trial coordination on behalf of Dr. Falk Pharma GmbH, ensures that all protocol amendments are forwarded to the participating trial centres.

All amendments that are likely to have an impact on the safety or rights of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, are substantial amendments and must be submitted to the relevant IECs/IRBs and CAs (where applicable) for application for a favourable opinion/approval prior to being initiated, except when the changes are necessary to eliminate immediate hazards to the subjects (in which case the implemented changes must be submitted afterwards as soon as possible).

Changes that involve only logistical or administrative aspects of the trial or other non-substantial amendments by the sponsor's judgment are not subject to favourable opinion/approval but have to be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment. Documentation of non-substantial amendments will also be available on request for inspection at the trial site or the sponsor premises as appropriate. The national ethical/regulatory requirements will be adhered to.

Amendments that might affect the health interests of the patients will require another informed consent. Administrative or technical changes, which do not affect the health interests of the patients, do not require a new vote by the IEC/IRB or a new informed consent from the patients already included in the trial.

Of note: For EU Member States, the above applies until having received authorisation for the transitioned trial via Clinical Trial Information System (CTIS). After authorisation of the transitioned trial in CTIS, clinical trials in EU member states will have to comply with the rules for requesting substantial and non-substantial modifications of the Regulation (EU) No 536/2014.

11 CASE REPORT FORM

CRO will develop an appropriate English electronic internet-based eCRF.

Each user is informed by the CRO of the clinical trial web-site internet address and is allocated a personal user account and a personal start-up password to access the confidential web site of the eCRF and the related IRT. The personal password must be kept confidential and must only be used by the person to whom it was assigned. New user accounts need to be requested for each new authorised user at the trial centre to ensure that each entry / change recorded in the audit trail can be allocated to the person who performed the entry / change.

Investigator or designated personnel will be trained how to enter all patients' data to be recorded in this trial. Investigators or designated personnel must enter the information required by the protocol into the eCRF. No questions left unanswered. For all countries, the eCRFs have to be completed in English. The investigator or designated personnel (i.e.,

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his/her deputy or another physician being part of the investigator`s team) must sign the data in the eCRF visit-wise in a timely manner.

Patient questionnaires and patient's diaries being part of the ePROM will be completed in patient's local language. Related data will be directly entered by patients into the ePROM-via a patient-individual web-access.

Reports from central laboratory will be made available in the eCRF on an ongoing basis by an up-load of related data using an electronic interface, as further specified in the eCRF completion guide.

External data that are made available in the eCRF do not need additional source documentation on site (see section 15.1 for further information). Nonetheless trial centres will receive central lab reports (in electronic portable document format [PDF]) in addition by e-mail, which should be printed out for filing in the patient's medical records. Finally, all data (i.e., those from external sources as well as those entered by the investigator or delegated person(s)) are considered part of the eCRF building up the clinical database for this trial.

The eCRFs have to be available at all times for monitoring visits. Monitors will review the eCRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. For corrections a reason must be provided. The eCRFs and related forms are saved immediately after entering the data by the investigator or delegated person(s). All data are stored in one central database at the eCRF provider while the trial is ongoing, and all data are stored at the responsible CRO for final analysis after database lock (DBL).

After trial completion, the trial centre will receive a Compact Disc (CD)/Digital Versatile Disc (DVD) with a compilation of the eCRF trial data including audit trail information per site and related forms (electronic PDF files), to be archived with its trial documents. Sponsor will receive electronic, bookmarked PDF files of individual eCRFs (including audit trail) including all related forms (central laboratory data and results from GEBT, patient's questionnaires and diaries as documented in the ePROM) for archiving (and if applicable a list of all queries and SAE forms.

12 QUALITY CONTROL AND QUALITY ASSURANCE

According to the ICH Harmonised Tripartite Guideline on Good Clinical Practice E6(R2) (ICH GCP) the sponsor is obliged to implement and maintain quality assurance and quality control systems with written SOPs to ensure that studies are conducted, and data are generated, recorded, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

12.1 Trial Management and Monitoring

The sponsor's responsible project manager will act as the central contact on the side of the sponsor and will supervise the overall conduct of the trial. The sponsor's project manager will be assisted in this by the CRO. Details of the responsibilities of the CRO regarding trial organisation, monitoring, data management, and statistical analysis are defined in a detailed contract between the CRO and the sponsor.

The ICH GCP and the Directive 2001/20/EC of April 4, 2001 (or following the transition of the trial: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, repealing Directive

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2001/20/EC), are intended to improve the quality of the various steps and activities in the conduct of a clinical trial. The responsibilities of the sponsor, monitors, and investigators are regulated in this directive (or following the transition of the trial in the CTR). The sponsor is obliged to set up a system to guarantee quality control at every stage in the conduct of the clinical trial.

Quality control includes (I) pre-trial visits for those centres who are unknown to the sponsor from previous studies, to ensure the general qualification of the centre and the potential trial personnel, (II) initiation visits to assure the medical and formal instruction of investigators as to the procedures and activities to be performed for this trial, (III) regular monitoring visits including checks of eCRF data on accuracy and completeness, formal and medical plausibility, correct handling of data and source data verification (SDV), and computer-based integrated range and consistency checks, (IV) regular central eCRF review of data completeness and accuracy, query resolution and safety aspects by using EDC reports, (V) regular site contact phone calls and/or remote monitoring, evaluating the current site situation, proper safety reporting, follow-up on outstanding action items and identifying issues. Every step of data handling and processing is subject to written procedures and has to undergo documented checks and supervision.

The investigators participating in the trial must allow the monitor to make regular visits. At these visits, the monitor will check the completeness, plausibility and consistency of the data recorded in the eCRF as well as compliance with the protocol and the correct handling and storage of the trial medication.

Details concerning the type and extent of SDV will be specified in the monitoring manual.

The investigator will allow the monitor to check the entries by comparison with the original patient documents (SDV, see also section 15.1). In the same way, other facilities involved (laboratories, specific examination sites, pharmacies) may be inspected.

12.2 Quality Assurance

Quality assurance (external audits and internal quality checks) must be carried out by an independent person not directly involved in the trial. All trial participants, the International Coordinating Investigator, National Coordinating Investigator(s), monitors, and statisticians will consent to this procedure. The investigators will agree to visits being made by the auditors and undertake to cooperate with the person conducting the audit. Audit reports and an audit certificate will be issued.

Formal quality checks (QC) will be done based on appropriate “Review Checklist and Approval Forms” to document the QC process and to provide formal approval of related documents.

At least the following audits and/or internal QCs are planned to be performed in this trial:

- On-site audits of 10% of recruiting trial centres,
- Audit/QC of the Clinical Trial Protocol,
- Audit/QC of the Patient Information and Informed Consent Form (PIIC),
- Audit/QC of eCRF,
- Audit of data management,
- Audit/QC of the Clinical Study Report.

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12.3 Risk Management

In correspondence to ICH Guideline for Good Clinical Practice E6(R2) a system to manage quality throughout all stages of the clinical trial process is installed. The quality management system uses a risk-based approach which focuses on trial activities essential to ensuring human subject protection and reliability of trial results. The methods used to assure and control the quality of a trial should be proportionate to the risks inherent in the trial and the importance of the information collected.

Throughout the life cycle of the trial the risk management includes the following procedures to manage risks effectively:

- Installation of a risk management team
- Risk identification and evaluation
- Definition of prevention and mitigation strategies
- Definition of risk indicators for centralised/remote monitoring
- Qualitative and quantitative analysis of the risks throughout the clinical trial
- Risk response

12.4 Serious Breaches

With the transition to Clinical Trials Regulation (EU) 536/2014 (Annex III, section 2.1 (2)), any deviation of the approved protocol version or the CTR that is likely to affect the safety, rights of trial subjects and/or data reliability and robustness to a significant degree in the clinical trial will be classified as a serious breach (for EU member states). Serious breaches will be reported to Dr. Falk Pharma GmbH by sites or vendors via the following email address: PPD and reported according to CTR (Regulation (EU) No. 536/2014). In parallel, the lead CRO will be informed by sites or vendor staff via the following e-mail address: PPD

The initial notification should include all available information on the suspected serious breach, and it should indicate the serious breach reporting deadline (i.e., not later than seven days of becoming aware of that breach). Additional information will be provided promptly to Falk Pharma GmbH and the lead CRO when it becomes available.

Of note: For participating countries outside of the EU reporting requirements for serious breaches might differ from the ones mentioned above (local requirements of the respective country should be respected).

13 ETHICAL CONSIDERATIONS

This trial will be conducted in conformity with the Declaration of Helsinki (in the latest relevant version accepted by the respective countries), international standards, and the respective national regulation (see section 14).

13.1 Patient Information and Patient's Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki (see section 14.1), the ICH Guidelines for GCP, and in accordance with all applicable laws and regulations (see section 14.2). The informed consent form and patient information sheet (PIIC) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of

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conducting the trial. The PIIC further explain the nature of the trial, its objectives, and potential risks and benefits as well as the date when informed consent is given.

Before being enrolled in the clinical trial, every patient will be informed that participation in this trial is voluntary and that he/she can withdraw from the trial at any time without giving a reason and without having to fear any loss in his/her medical care.

The patient will be informed about the IMP and the possible side effects. At the same time the investigator will explain the purpose, significance, and scope of the trial, and inform the patient about the insurance protection and the obligations of the insured.

The patient will have sufficient time and opportunity to clarify any unresolved questions. Furthermore, the patient will be handed over a ”Patient Information Form” containing all the important information in written form (in local language) and the signed informed consent. The patient’s consent must be obtained in writing before the start of the trial. By signing the informed consent, the patient declares that he/she is participating voluntarily and intends to follow the trial protocol instructions and the instructions of the investigator, and to answer the questions asked during the course of the trial.

The investigator will keep an original of the written patient informed consent in the designated place in the investigator’s file.

13.2 Independent Ethics Committees/Institutional Review Boards and National Competent Authorities

In conformity with the national guidelines and the GCP provisions, the trial protocol, the patient information/informed consent form and any other document given to the patient has been submitted to an IEC/IRB before the start of the trial. The clinical trial in each of the participating countries will only start after having received an initial ethics approval.

Furthermore, no patient will be/has been included in the trial before the respective requirements of the national competent authorities are/were fulfilled.

14 LEGAL BASES

The trial has to be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

14.1 Declaration of Helsinki

The trial will be carried out in conformity with the “Ethical principles for medical research involving human subjects” of the 18th World Medical Association (WMA) General Assembly in Helsinki 1964, and amended by the 29th, 35th, 41st, 48th, 52nd WMA General Assemblies (Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000) and the Note of Clarification on Paragraph 29 added by the 53rd WMA General Assembly, Washington 2002, the Note of Clarification on Paragraph 30 added by the 55th WMA General Assembly, Tokyo 2004, the 59th WMA General Assembly, Seoul 2008, and the 64th WMA General Assembly, Fortaleza, Brazil 2013. The applicable version for the respective country will be taken into consideration.

14.2 Other Legal Bases

The other legal bases of this clinical trial are as follows:

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- ICH Harmonised Guideline for Good Clinical Practice E6(R2) (2017)
- Directive 2001/20/EC (April 4, 2001), or following the transition of the trial: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- Commission Directive 2005/28/EC (April 8, 2005)
- National regulatory requirements/guidelines of the participating countries concerning Clinical Trials

The coordinating investigator and all investigators will be given an up-to-date IB containing full detail of the status of the pre-clinical and clinical knowledge of the trial medication. As soon as new information is obtained, an updated version or an amendment to the existing IB will be supplied.

15 RESPONSIBILITIES

The sponsor, the investigators, and all involved trial personnel agree to conduct this clinical trial in accordance with the ICH Guideline for GCP.

15.1 Direct Access to Source Documents According to ICH GCP

According to ICH-GCP, the investigator(s)/institution(s) must provide direct access to source data/documents for trial related monitoring, audits, Ethics Committee review, and regulatory inspection. Each patient will have consented - via written informed consent - to direct access to his/her original medical records for trial-related monitoring, audit, Ethics Committee review, and regulatory inspection.

Trial monitors will perform ongoing SDV to confirm that critical protocol data entered into the eCRFs by authorised site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X rays, patient files, and records kept at pharmacies, laboratories, and medico technical departments involved in a clinical trial.

At least the following data must be recorded in the patient’s medical records or must be included in the patient’s medical record:

- Note that the patient is participating in this trial (including the study number and the screening number),
- Date of given written informed consent,
- Date of each on-site visit
- Demography of the patient (name, address, birthday, sex)
- Height (at BSL, V2) and weight,
- Vital signs by visit
- Underlying trial disease (IODG), date of the first symptoms and of first diagnosis of trial disease, including details on current symptoms

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- History of major gastrointestinal surgeries
- Dates and results of previous diagnostic measurements (i.e., UGE, abdominal sonography, MRI, or CT) within the last 12 months, if applicable
- General medical history and concomitant diseases
- Gastroparesis related diets (for the last 3 months prior to BSL (V2) and up until end of the trial [EOS/FU, V7])
- Previous (over the last 3 months prior to BSL, V2) and concomitant medications
- Dates (and times) of examinations carried out in this trial (UGE and abdominal sonography, MRI, or CT [if applicable], GEBT, ECG, laboratory sampling)
- Date of randomisation
- Dates of IMP dispense (incl. medication kit numbers) and IMP return
- Results from diagnostic measurements carried out in this trial (UGE and abdominal sonography, MRI, or CT [if applicable]),
- All laboratory findings (print-out of the local and central laboratory)
- Printouts of results from GEBTs
- Printouts of ECG measurements
- EQ-5D-5L questionnaires completed by patients
- (Serious) AEs or ADRs,
- Reason for discontinuation, if applicable.

Investigator's questionnaires directly answered in the eCRF (i.e., no prior written or electronic record of the data) are considered to be source data and does not need additional documentation in the patient's medical records.

15.2 Archiving of Essential Documents

15.2.1 Investigator

The investigator has to maintain a filing system for all documents relevant to the trial, such as the CD/DVDs of the eCRFs, the written informed consents, paper copies of questionnaires, the patient identification list, the patient records with the original data, drug dispensing log, and the investigator's trial file for a minimum of 25 years, but at least two years longer than the product is on the market in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. Therefore, the responsible monitor will ensure at the close-out visit that on each binder of the Investigator Site File (ISF) the date until when the binder and its content has to be archived will be printed and highlighted.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (ICH GCP, 4.9.5).

At the end of this period, the investigator needs to obtain written permission from the Sponsor when the study related records are no longer needed and before any of the documents are destroyed.

The investigator/institution will notify the Sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

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Patient's (hospital) records will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution, or private practice. Where the archiving procedures do not meet the minimum timelines required by the Sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The contract with the investigator/institution will contain further details regarding record keeping and archiving relevant for the study site.

15.2.2 Sponsor

All printouts and electronic files of the eCRF data and all other documentation pertaining to the trial will be kept by Dr. Falk Pharma GmbH for a minimum of 25 years, but at least two years longer than the product is on the market in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements.

Samples of the IMP will be kept for one year after the expiry date but at least until the end of the trial.

16 INSURANCE

In conformity with the ICH Guidelines, Dr. Falk Pharma GmbH has taken out insurance policies prior to the enrolment of the first patient in each respective country.

The patient will be informed by the investigator on the provisions of the relevant insurance policy. Under the terms of the insurance, it is an obligation of the patient during the clinical trial not to undertake any other medical treatment without the consent of the investigator (besides in a case of emergency), not to take part in any other clinical trial and to report health injury which could have occurred as a result of the clinical trial, to the investigator and the insurance company without delay.

17 PATIENT DATA AND DATA PROTECTION

The name of the patient and other personal patient data will at no time be disclosed to Dr. Falk Pharma GmbH. Besides the trial-related data, Dr. Falk Pharma GmbH will be given only pseudonymised data of the patient from the eCRF or questionnaires. If it becomes necessary to identify the patient's name for medical reasons during the course of the trial, the staff will be bound to observe confidentiality and to comply with the state-specific data protection law.

If, in order to comply fully with responsibilities and with the imposed duty to notify, personal details of the patient are stored and processed, organisational measures to prevent their disclosure to unauthorised third parties must be taken for reasons of data protection. The relevant provisions of the state-specific data protection legislation will be met.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data.

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18 CONFIDENTIALITY

This protocol, information containing the eCRF, other results forms, and laboratory data must be handled with strict confidentiality and not be disclosed to third parties except with the express prior consent of Dr. Falk Pharma GmbH. Furthermore, all information concerning the trial drugs and Dr. Falk Pharma GmbH operations (e.g., patent applications, formulas, manufacturing processes, formulation information) supplied by Dr. Falk Pharma GmbH and not previously published, are considered confidential and shall remain the sole property of Dr. Falk Pharma GmbH. In particular, it must be ensured that the trial medication is kept out of reach of third parties. Staff of the centre's principal investigator involved in this trial is also bound by this agreement.

19 SUMMARY OF THE RESULTS, FINAL REPORT AND PUBLICATION

The responsible biometrician and/or medical writer will produce a final integrated CSR in conformity with the "Note for guidance on structure and content of clinical trial reports" (CPMP/ICH/137/95 (FINAL) 1995) and the "Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications" (CHMP/EWP/2998/03 (FINAL) 2004).

The final integrated CSR will be signed by the coordinating investigator, the responsible biometrician, and the sponsor and passed on to Dr. Falk Pharma GmbH. The coordinating investigator will receive a copy of the final report.

Beside the fully integrated CSR a summary of the results of the clinical trial as well as a summary for laypersons will be submitted to the MSCs within one year after the end of the trial in the EU in accordance with the CTR (Regulation (EU) No. 536/2014). If the end of trial globally (EU and non-EU) should be later than the end of trial in the EU, the summary might be delivered later than within one year following end of trial in the EU, but as soon as possible, in order to include all data collected globally to ensure relevance of the statistical analysis.

Publication(s) and/or presentation(s) of the trial results is encouraged after appropriate time for review and written agreement by Dr. Falk Pharma GmbH. Dr. Falk Pharma GmbH has to be provided with a draft of the abstract and/or manuscript for review, editorial comments, and approval at least 30 days prior to submission and/or presentation. Neither the sponsor nor the coordinating investigator has the right to prevent publication, except for patent or copyright reasons.

The trial will be registered in a public data base (e.g., the EU Drug Regulating Authorities Clinical Trials Database) according to local regulations.

It is intended that the results of the trial as a whole are published before the results of subgroup populations will be presented or published. The first author will be chosen by the International Trial Coordinator in consultation with the sponsor. The number of co-authors will depend on the journal chosen for publication. The list of co-authors will be assembled according to the number of patients randomised by an investigational centre into this trial and completed according to this Clinical Trial Protocol.

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20 PAYMENT

Agreements about appropriate payment will be made between Dr. Falk Pharma GmbH and the investigators. These relate to the number of patients as well as the cost of clinical visits, laboratory investigations, and other services outside of normal routine examinations and specifically connected with the conduct of the trial, including an appropriate payment for trial documentation and administrational activities. The agreement will cover payment of eCRFs completed fully in conformity with the protocol. The investigator fee for patients who withdraw prematurely from the trial will be on a *pro rata* basis.

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22 APPENDICES

A - Investigator Signature Page (template)
B – List of changes with Amendments

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Appendix A: Investigator Signature Page (template)

Title	Double-blind, randomised, placebo-controlled, dose-finding phase IIb trial to evaluate the efficacy, safety, and tolerability of a 12-week-treatment with Naronapride in adult participants with at least moderate idiopathic or diabetic gastroparesis
Test drug	Naronapride 10/20/40 mg film-coated tablets
Reference drug	Naronapride placebo film-coated tablets
Trial Code	NAT-19/GPX
Protocol Version	Integrated Clinical Trial Protocol - Final Version 3.0 / 07.10.2024

SIGNATURE

I have read this protocol. I confirm that it contains all the information necessary to conduct this trial.

Additionally, I confirm that I will not start any trial related activities prior to having read the Investigator's Brochure and being informed about possible risks of this trial.

I hereby ensure that I have good knowledge of the ICH GCP Guideline E6 "Note for Guidance on Good Clinical Practice", of the World Medical Association Declaration of Helsinki „Ethical Principles for Medical Research Involving Human Subjects" and the most relevant national laws and regulations concerning clinical trials of participating countries.

I declare that I will conduct the clinical trial in accordance with the ICH GCP Guideline, the Declaration of Helsinki, and the most relevant national laws concerning clinical trials.
I will perform the trial and related activities according to protocol.

☐ Principal Investigator ☐ Sub-Investigator
☐ Deputy Investigator (if applicable)

Name: _____
(Please print)

Country, City: _____
(Please print)

_____ _____
Signature Date

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Appendix B: List of Changes with Amendments

List of Changes with integrated Clinical Trial Protocol – Final Version 2.0 / 21.12.2023

In order to harmonise the clinical study protocol across all countries involved in this clinical trial, the changes made with the Local Amendment 01 for Germany, Local Amendment 01 for France, Local Amendment 01 for UK and Switzerland, and Local Amendment 02 for UK as well as changes made in order to address responses to deficiency letters of the German IEC as well as Belgian and Italian authorities have now also been implemented globally with this Amendment, resulting in an integrated Clinical Trial Protocol Version 2.0 / 21.12.2023. The changes made to meet the local Amendments and aspects addressed in the response letters are detailed in the table below.

Based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent Regulation (EU) 536/2014, these changes are considered to be substantial because they significantly impact the safety, rights or physical/mental integrity of subjects.

Change	**CSP sections affected**	**Original Text (CSP v1.0 / 25.03. 2022)**	**Revised Text (CSP v2.0 / 21.12.2023)**	**Rationale**
Computer tomography (CT) described as only applicable if part of the clinical routine in the respective participating country (e.g., not applicable as study procedure in Germany, Switzerland, and UK).	Synopsis - Inclusion Criteria and Section 3.1.1 - Inclusion Criteria	9. No evidence of intestinal stenosis as determined by an imaging technique (i.e., either abdominal sonography, Magnetic resonance imaging [MRI] or imaging by computed tomography [CT] during screening phase (previous MRI/CT imaging or sonography results within 12 months prior to SCR 1 (visit 0) are acceptable, if	9. No evidence of intestinal stenosis as determined by an imaging technique (i.e., either abdominal sonography, ~~M~~magnetic resonance imaging [MRI] or imaging by computed tomography [CT; during screening phase (previous MRI/CT ~~imaging~~ or sonography results within 12 months prior to SCR 1 (visit 0) are acceptable, if	CT in Germany, Switzerland, and United Kingdom is not used as a routine diagnostic procedure to exclude intestinal stenoses. Updated based on the objection raised by the German IEC, and due to constraints imposed by the competent authorities prior

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03. 2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
		no relevant changes occurred in patient's disease status since that time),	no relevant changes occurred in patient's disease status since that time), **Note: CT to be performed only, if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK])**	to submission of the clinical trial in Switzerland and UK.
	Flow Chart - Footnote 5	5 Sonography/Imaging only to be performed, if no previous sonography/imaging has been performed within the last 12 months prior to SCR 1 (V0), provided that no relevant changes in disease status occurred since that time.	5 Sonography/Imaging only to be performed, if no previous sonography/imaging has been performed within the last 12 months prior to SCR 1 (V0), provided that no relevant changes in disease status occurred since that time. **CT as possible imaging procedure only to be performed during the screening phase if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK].**	
	Section 1.4 - Benefit/Risk Assessment	[...] N/A	[...] **Furthermore CT in this trial will only be performed, if part of the clinical routine to**	

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03. 2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
			detect intestinal stenosis in the respective participating country.	
	Section 6.2 - Overview of Time Sequence - 3rd Paragraph	These may include an UGE as well as an abdominal sonography or MRI or CT according to the usual routine at trial site, if not performed in the 12 months prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.	These may include an UGE as well as an abdominal sonography or MRI or CT **(CT to be performed only, if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK])** according to the usual routine at trial site, if not performed in the 12 months prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.	
	Section 6.3.1 - Screening Visit 1 (SFR 1; V0)	[..] • Abdominal sonography or MRI or CT, during the first two weeks of the screening phase, see section 6.4.9 [..]	[..] • Abdominal sonography or MRI or CT **(CT to be performed only, if part of the clinical routine in the respective participating**	

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03. 2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
			country), during the first two weeks of the screening phase, see section 6.4.9 [..]	
	Section 6.4.9 - Abdominal Sonography or MRI or CT - 1st Paragraph	To exclude intestinal stenosis an abdominal sonography, MRI, or CT during the first two weeks of the screening phase needs to be performed only, if no previous MRI/CT imaging or sonography has been done in the last 12 month prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.	To exclude intestinal stenosis an abdominal sonography, MRI, or CT **(CT to be performed only, if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK])** during the first two weeks of the screening phase needs to be performed only, if no previous MRI/CT imaging or sonography has been done in the last 12 month prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.	

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Change	**CSP sections affected**	**Original Text (CSP v1.0 / 25.03. 2022)**	**Revised Text (CSP v2.0 / 21.12.2023)**	**Rationale**
Clarification of inclusion criterion 6 to demonstrate that only patients with at least moderate activity are included in the trial.	Synopsis - Inclusion Criteria and Section 3.1.1 - Inclusion Criteria	6. Average weekly total symptom score of the ANMS GCSI-DD ≥2.0 based on the daily symptom scores recorded for at least 5 of 7 consecutive days in the week prior to BSL (visit 2),	6. Average weekly total symptom score of the ANMS GCSI-DD ≥2.0 **(i.e., demonstrating at least moderate severity of gastroparesis symptoms)** based on the daily symptom scores recorded for at least 5 of 7 consecutive days in the week prior to BSL (visit 2),	Updated based on the objection raised by Italian's Medicines Agency (AIFA).
Addition of precautionary measures for patients regarding a possible phototoxicity of naronapride.	**New Section 5.9 added** - Special precautions and warnings for use	N/A	**As a recently performed in vitro study on phototoxicity does not exclude naronapride of being phototoxic in humans, patients are requested to take precautionary measures to protect their skin from sunlight (e.g., the use of sunscreens, wearing of hats and long-sleeve garments) during the treatment with naronapride and for at least 5 half-lives (corresponding to for at least 3 weeks) after**	Results from an *in vitro* test regarding the phototoxicity of naronapride (as detailed in section 4.3.6 of the IB) do not exclude naronapride of being phototoxic in humans and therefore will be further evaluated *in vivo*. Updated based on the objection raised by the National Agency for the Safety of Medicines and Health Products in France (L'Agence nationale de sécurité du medicament et

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03. 2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
			taking the last dose of the IMP. **Additional information is provided in the corresponding IB.**	des produits de santé, ANSM).
In the original CSP 1.0, dated 25.03.2022, one of the stopping criteria for the study was defined as ocurrence of similar serious ADRs in more than 10% of the planned study population.	Section 8.2.1 - Termination of the Whole Trial *Of note: In the orginal Clinical Trial Protocol, version 1.0, dated 25.03.2022, the numbering of subchapters was incorrect (8.1.1 and 8.1.2 instead of 8.2.1 and 8.2.2.). This will be*	Moreover, if an unexpected, serious, or unacceptable risk to subjects enrolled in the study is discovered, the Sponsor must terminate or interrupt the trial, especially in the following cases: • ... • If a serious ADR with the same reaction term (preferred term [PT]) occurs in more than 10% of the planned study population, i.e., in more than 32 patients, • …	Moreover, if an unexpected, serious, or unacceptable risk to subjects enrolled in the study is discovered, the Sponsor must terminate or interrupt **(temporary halt)** the trial, especially in the following cases: • ... • If a serious ADR with the same reaction term (preferred term [PT]) occurs in more than **5%** of the planned study population, i.e., in more than **16** patients, • …	The originally chosen threshold of 10% of patients was based on the valid upper limit for common side effects (1-10%) in order not to jeopardize patient's safety on the one hand, but on the other hand to obtain sufficient data to be able to make a well-founded assessment of an occurring side effect. However, with this Amendment the upper limit is lowered to 5% considering the longer duration of treatment with naronapride, for which clinical data are not yet available, so a lower threshold seems to be

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03. 2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
	corrected as part of the current amendment.			justified Updated based on the objection raised by the Medicines & Healthcare products Regulatory Agency (MHRA) in UK.
Addition of safety definitions	Section 7.1.2 - Serious Adverse Events	A serious adverse event (SAE) is any untoward medical occurrence that at any dose: •Results in death, •Is life-threatening, •Requires in-patient hospitalisation or prolongation of existing hospitalisation, •Results in persistent or significant disability/incapacity, •Is a congenital anomaly/birth defect, •Meets the definition of other medically important conditions	A serious adverse event (SAE) is any untoward medical occurrence **or effect in a patient or clinical investigation subject administered a pharmaceutical product and may or may not have a suspected causal relationship to the IMP and which is serious, i.e.,** that at any dose: •Results in death, •Is life-threatening, •Requires in-patient hospitalisation or prolongation of existing hospitalisation, •Results in persistent or significant disability/incapacity,	Addition of safety definitions (SAR, 'suspected' SAR, SUSAR, (SAE)) based on the request raised by the competent authority in Belgium (Federal Agency for Medicines and Health Products [famhp).

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03. 2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
			•Is a congenital anomaly/birth defect, •Meets the definition of other medically important conditions	
	New section 7.1.3.3 added - (Suspected) Serious Adverse Reaction	N/A	**The definition of Serious Adverse Reaction (SAR) includes all SAEs where a causal relationship between SAE and IMP (at any dose) is suspected by either sponsor or investigator.** **Some medical events may jeopardize the subject or may require an intervention to prevent one of the characteristics/consequences for seriousness. Such important medical events should also be considered as serious.**	

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03. 2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
	Section 7.1.3.4 (former section 7.1.3.3) - Suspected Unexpected Serious Adverse Reaction	The definition of Suspected Unexpected Serious Adverse Reaction (SUSAR) includes a suspected causal relationship with administration of the IMP (thus, a causality assessment of "unlikely" or "not related" is not a SUSAR).	**A Suspected Unexpected Serious Adverse Reaction (SUSAR) refers to SAR case reports, which are not consistent with the RSI in the current version of the IMP's IB.** ~~The definition of Suspected Unexpected Serious Adverse Reaction (SUSAR) includes a suspected causal relationship with administration of the IMP (thus, a causality assessment of "unlikely" or "not related" is not a SUSAR).~~	
Maximum retention period for optional blood samples has been added.	Section 6.4.6.2 – Sampling for Future Trial-Related Scientific Investigations - Optional	The samples are planned to be archived for those possible investigations under responsibility of Dr. Falk Pharma GmbH at the central laboratory for up to 5 years after obtaining marketing authorisation of naronapride for the treatment of gastroparesis in any country worldwide. In case, no marketing authorisation can be	The samples are planned to be archived for those possible investigations under responsibility of Dr. Falk Pharma GmbH at the central laboratory for up to 5 years after obtaining marketing authorisation of naronapride for the treatment of gastroparesis in any country worldwide **(for a maximum of up to 10 years after the end**	Updated for reasons of harmonisation with modified wording in the ICF based on the objection raised by the German IEC (*retention periods have to be stated explicitly and unambiguously*).

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03. 2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
		obtained, or the development program is withdrawn, samples will be destroyed immediately afterwards.	**of trial)**. In case, no marketing authorisation can be obtained, or the development program is withdrawn, samples will be destroyed immediately afterwards.	

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Since this clinical trial initially approved under CTD is expected to remain active with at least one trial site in the EU beyond January 30, 2025, a transition of this trial to CTR will be necessary. Consequently further changes have been implemented in the integrated Clinical Trial Protocol Version 2.0 / 21.12.2023 in order to meet the requirements of the CTR (Regulation (EU) No. 536/2014) following the transition of the trial. These changes do only apply to EU member states.

Based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent Regulation (EU) 536/2014, these additional changes are considered to be non-substantial (changes do neither significantly impacts the safety, rights or physical/mental integrity of subjects nor the scientific value of the trial).

Change	**CSP sections affected**	**Original Text (CSP v1.0 / 25.03.2022)**	**Revised Text (CSP v2.0 / 21.12.2023)**	**Rationale**
The EudraCT No. has been supplemented by the EU CT No.	Header Title page Synopsis Protocol signatures Appendix A Appendix B *New* Appendix C	EudraCT No.: 2021-002254-86	EudraCT No.: 2021-002254-86 **EU CT No.: 2023-510195-31**	In preparation for the transition of this clinical trial from CTD to CTR, the clinical trial has been registered under CTIS
In line with the CTR dimenhydrinate and cyclizine have now been classified as rescue medication / Auxiliary Medicinal Products	Synopsis - *New Section* 5.6.2 'Auxiliary Medicinal Product'	N/A	**Locally sourced OTC-preparations against nausea (preferably dimenhydrinate, or, if not available in the respective country, alternatively cyclizine or**	According to CTR (I Legislative acts; (54)): *"[..] a distinction should be made between investigational medicinal products (the tested product and its*

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
(AMPs). Since the approval situation in the participating countries might change at any time, depending on the local availability of dimenhydrinate and cyclizine, meclozine has also been allowed as a rescue medication. In this context, the wording was formulated more generally (not only applicable for the Netherlands). Consequently, exclusion criterion 19 has been adjusted accordingly.	Synopsis – Exclusion Criteria Section 3.1.2 – Exclusion Criteria	19. H1-receptor antihistamines of first generation (e.g., doxylamine) within 2 weeks prior to BSL (visit 2) Note: dimenhydrinate (cyclizine in the Netherlands, only) in the standard daily prescribed dose is allowed if not applied for more than 2 days per week in the two weeks prior to BSL (visit 2),	**meclozine) as rescue medication in the standard daily prescribed dose are allowed if not applied for more than 2 days per week from SCR 2 (V1) onwards and during the DBT phase until EOT/WD (V6).** 19. H1-receptor antihistamines of first generation (e.g., doxylamine) within 2 weeks prior to BSL (visit 2); **Exception: Locally sourced OTC preparations against nausea (preferably** dimenhydrinate**, alternatively** cyclizine **or meclozine) as rescue medication** in the standard daily prescribed dose are allowed if not applied for more than 2 days per week	*reference products, including placebos) and auxiliary medicinal products (medicinal products used in the context of a clinical trial but not as investigational medicinal products), such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial."* As the CSP specifies that the use of dimenhydrinate /cyclizine/meclozine to alleviate symptoms associated with gastroparesis

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
Furthermore, the wording regarding the use of dimenhydrinate/cyclizine/ meclozine as rescue medication/AMP has been updated throughout the protocol.	Flow Chart including Footnotes 12 and 13 Section 5.6 – Concomitant Medications and Auxiliary Medicinal Products *New* Sections 5.6.1 – 5.6.3 Section 6.2 – Overview of Time Sequence Sections 6.3.2 – 6.3.5 Section 6.4.12 – Patient Questionnaire		**from SCR 2 (visit 1) onwards**, Individual changes can be traced back via track change mode (see CSP sections affected).	is to be done according to the instructions of the protocol, i.e., in the context of the clinical trial, those drugs have now been (re)defined to rescue medication/AMP. With the introduction of this definition, it has also been clarified that the AMP will be sourced locally to ensure that the associated package leaflets are available in the local languages.

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
	and Patient's Diaries including Section 6.4.12.1 Section 6.4.12.6 Section 9.3.8 – Missing Values			
Protocol synopsis was supplemented by ethical considerations relating to the clinical trial including the expected benefit to the individual subject or group of patients represented by the trial subjects as well as the nature and extent of burden and risk.	Synopsis – *New section* 'Benefits and expected risks'	N/A	**Benefits and expected risks** Complete text as given in the respective section of the synopsis newly introduced.	According to CTR Q/A (5.8 Question: What should be included in the protocol summary described in Annex I, D. 24 / point 9.), *"Ethical considerations related to the clinical trial, including the expected benefits for the individual subject or the patient group represented by the subjects and the nature and extent of burdens and risks"* should be included in the protocol synopsis and had to be

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
				supplemented accordingly.
A description of the recruitment procedures has now been added to the definitions of 'Patient Selection'.	Section 3.1 – Patient Selection	N/A	**The Investigator should only include patients who meet all eligibility criteria, are not put at undue risk by participating in the trial and can be expected to comply with the protocol.** **Eligible patients according to inclusion and exclusion criteria will be identified by search in the patient pool already available at the investigational site or will be recruited from the population seen at the investigational sites in clinical routine. The Investigator will contact potential participants when they are presenting at the site for routine treatment of their gastroparesis. In addition, investigators may**	To comply with the CTR (Annex I, Section D. Protocol; 17. (z)) "*a detailed description of the recruitment [..] procedure"* had to be included in the CSP.

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
			ask colleagues for help in referring suitable patients for the clinical trial, using an appropriate and approved referral letter. Furthermore, advertising may be considered (once required approvals are in place for advertisements at respective sites).	
Former definitions of 'Clinical Trial' and 'Clinical Study' have been re-defined according to CTR.	Section 4 – Trial Design	The interventional study (shortly study or trial; both terms are used synonymously) will be conducted with four treatment groups [..]	The **clinical trial** will be conducted with four treatment groups [..]	According to CTR (I Legislative acts; (3)): *"The existing definition of a clinical trial as contained in Directive 2001/20/EC of the European Parliament and of the Council should be clarified. For that purpose, the concept of clinical trial should be more precisely defined by introducing the broader concept of 'clinical study' of which the clinical trial is a category. That category should be defined on the basis of specific*

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				criteria. This approach takes due account of international guidelines, and is in line with the Union law governing medicinal products, which builds on the dichotomy of 'clinical trial' and 'non-interventional study" the term "Clinical trial" needed to be re-defined. See also Article 2(1) and (2) for definitions of 'Clinical Study' and 'Clinical Trial' according to CTR.
The definition of medication error has been specified in accordance with the definition as given on the website of the European Medicines Agency (EMA). Furthermore, misuse and abuse have been added to the events that have to be	Section 7.1.5 – Medication Errors/Misuse/ Abuse	Inappropriate schedule of product administration where a clinical consequence occurred should be recorded based on investigator judgement. Treatment non-compliance (incl. missed doses) where no clinical consequence occurred should not be recorded as medication errors.	**A medication error refers to any unintentional error and/or failure in the dispensing or administration of the IMP that can be harmful for a patient. Medication errors include accidental overdose or underdose, inappropriate schedule of product**	According to CTR (Annex III [SAFETY REPORTING] 2.1 Adverse Events and Causality, 2.: *"Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same*

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documented by the investigator and notified to the Sponsor. For EU member states reporting obligations for the time after transition to CTR have been implemented.		In addition, any clinical consequences of the medication error must be recorded as separate AEs. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required.	**administration, incorrect route of product administration, wrong product administered, and expired or quality diminished product administered.** Treatment non-compliance (incl. missed doses) where no clinical consequence occurred should not be recorded as medication errors. **Medication errors, misuse or abuse in relation to the IMP should be documented as AE by the investigator and notified to the sponsor.** In addition, any clinical consequences of the medication error**, misuse or abuse** must be recorded as separate AEs. If the AE originating from the medication error**, misuse or abuse** qualifies as an SAE,	*obligation to report as adverse reactions.”),* the handling of medication errors pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP needed to be adapted to fulfil the requirements of the CTR.

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			expedited reporting is required.	
Provisions/guidelines to be followed by the Investigator for reporting AEs and SAEs were specified according to CTR requirements.	Section 7.2.2 *New* Section 7.2.2.1 – Investigator's Reporting Responsibili-ties for SAEs	7.2.2 Documentation and Reporting of Serious Adverse Events [..] Any SAE (including death, irrespective of the cause) occurring during the screening phase, the double-blind treatment phase, or follow-up phase must be reported by the investigator immediately (without undue delay) after it comes to light to the project manager of the CRO and in parallel to the Sponsor's Drug Safety, [..].	**7.2.2.1 Investigator's Reporting Responsibilities for SAEs** [..] Any SAE (including death, irrespective of the cause) occurring during the screening phase, the double-blind treatment phase, or follow-up phase must be reported by the investigator **to the project manager of the CRO and in parallel to the Sponsor's Drug Safety** immediately (without undue delay **but not later than 24 hours**) after it comes to light~~ to the project manager of the CRO and in parallel to the Sponsor's Drug Safety~~, [..].	To be in line with the CTR (Article 41; 2.: *"The investigator shall report serious adverse events to the sponsor without undue delay **but not later than within 24 hours** of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required.")* the timeframe for SAE reporting had to be amended accordingly.

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Reporting responsibilities of the Sponsor regarding SUSARs were specified according to CTR requirements. Changes associated with the transition to CTR required restructuring and further supplementations to the chapter.	Section 7.2.2 *New* Section 7.2.2.2 – Reporting Responsibili-ties of the Sponsor	7.2.2 Documentation and Reporting of Serious Adverse Events [..] Suspected adverse drug reactions (ADRs) following other drugs than the IMP will not be reported to authorities, ethics committees, or investigators by the sponsor. Investigators are obliged to report these suspected adverse drug reactions to the responsible marketing authorisation holder or the CA of the country where the reaction occurred. In case the sponsor becomes aware of such an event, the information will be provided to the responsible marketing authorisation holder of the concerned product. SUSAR reporting to the German CA and EMA will be	**7.2.2.2 Reporting Responsibilities of the Sponsor** [..] **The sponsor's DSM is responsible for assessing whether an SAR is expected in accordance with the Reference Safety Information (RSI) as provided with the most current version the IB.** **SUSARs for the EU/European Economic Area (EEA) countries will be reported to EudraVigilance. The Sponsor is responsible for reporting SUSARs to EudraVigilance. Reporting SUSARs to Ethics Committees in the EU/EEA countries is contractually delegated to the coordinating CRO. A SUSAR report has to be approved by the**	According to CTR (Annex I, Section D. Protocol; 20. (c) the protocol shall describe the procedures for "*reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database*".

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		performed by the sponsor's DSM. In case, a country of the European Union requires additional notification (in addition to EMA notification), the CRO will perform this national notification. SUSAR reporting to the CAs outside of the European Union will be performed by the CRO according to national/local requirements. For all countries, the CRO will inform all investigators. The CRO or the investigator (as applicable) will inform the Leading IECs according to national/local requirements, after the report has been reviewed and approved by the sponsor's DSM. [..] The reporting of AEs and SAEs will be performed according to current Standard	**Sponsor's Drug Safety Officer before sending it to EudraVigilance and the Ethics Committee(s).** **SUSAR reporting to the CAs outside of the European Union will be performed by the CRO according to national/local requirements.** **For all countries, the CRO will inform all investigators. The CRO or the investigator (as applicable) will inform the Leading IECs according to national/local requirements, after the report has been reviewed and approved by the sponsor's DSM**. ~~Suspected adverse drug reactions (ADRs) following other drugs than the IMP will not be reported to authorities, ethics committees, or investigators by the sponsor. Investigators are obliged to~~	

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		Operation Procedures (SOPs) of Dr. Falk Pharma GmbH: • SOP CR-409: Reporting of Adverse and Serious Adverse Events in Clinical Studies	~~report these suspected adverse drug reactions to the responsible marketing authorisation holder or the CA of the country where the reaction occurred. In case the sponsor becomes aware of such an event, the information will be provided to the responsible marketing authorisation holder of the concerned product.~~ ~~SUSAR reporting to the German CA and EMA will be performed by the sponsor's DSM. In case, a country of the European Union requires additional notification (in addition to EMA notification), the CRO will perform this national notification. SUSAR reporting to the CAs outside of the European Union will be performed by the CRO according to national/local~~	

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			~~requirements.~~ ~~For all countries, the CRO will inform all investigators. The CRO or the investigator (as applicable) will inform the Leading IECs according to national/local requirements, after the report has been reviewed and approved by the sponsor's DSM.~~ [..] ~~The reporting of AEs and SAEs will be performed according to current Standard Operation Procedures (SOPs) of Dr. Falk Pharma GmbH:~~ • ~~SOP CR-409: Reporting of Adverse and Serious Adverse Events in Clinical Studies~~ **The reporting of AEs and SAEs will be performed according to ICH GCP, CTR**	

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			(Regulation (EU) No 536/2014) (for EU member states following the transition of the trial), national/local requirements (Non-EU member states) and current Standard Operating Procedures (SOPs) of Dr. Falk Pharma GmbH (or CRO internal SOPs for processes not covered by Sponsor SOPs).	
A general information regarding temporary halt/termination of the trial has been given in section 8.2 to introduce a reference for rules to be followed by EU member states after transition of the trial to CTR. Furthermore the phrase "to interrupt the trial" has been specified as "temporary halt" in section 8.2.1.	Section 8.2 – Criteria for the Termination of the Trial Section 8.2.1 – Termination of the Whole Trial	8.2 Criteria for the Termination of the Trial 8.2.1 Termination of the Whole Trial [..] Moreover, if an unexpected, serious, or unacceptable risk to subjects enrolled in the study is discovered, the Sponsor must terminate or interrupt the trial, especially in the following cases:	8.2 Criteria for the Termination of the Trial **The Sponsor may decide to temporarily halt the trial, to terminate the whole trial, parts of the trial or to discontinue an individual investigational site at any time.** **Of note: After transition of the trial, EU member states should follow general rules for temporary halt,**	General rules for temporary halt, premature termination or suspension of the trial to be followed by EU member states after transition of the trial are defined in CTR (Articles 37 and 38).

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		[..]	**premature termination or suspension of the trial defined by CTR (Regulation (EU) No. 536/2014; in particular Articles 37 and 38).** 8.2.1 Termination of the Whole Trial [..] Moreover, if an unexpected, serious, or unacceptable risk to subjects enrolled in the study is discovered, the Sponsor must terminate or interrupt **(temporary halt)** the trial, especially in the following cases: [..]	
Taking into account that not only aspects that affect the patient's safety, but also their rights, may require a substantial amendment, the definition of a substantial	Section 10 – Protocol Amendment(s)	[..] Pursuant to EU-Guideline "CT-1" (2010/C82/01) all amendments that are likely to have an impact on the safety of the trial subjects or to change	[..] "~~Pursuant to EU-Guideline "CT-1" (2010/C82/01) a~~**All** amendments that are likely to have an impact on the safety **or rights** of the trial subjects	To be in line with the definitions as given in Article 2, 2. (13) of the CTR ("*Substantial modification' means any change to any aspect of the clinical trial*

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amendment has been supplemented accordingly.		the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, are substantial amendments and must be submitted to the relevant IECs and CAs (where applicable) for application for a favourable opinion/approval prior to being initiated, except when the changes are necessary to eliminate immediate hazards to the subjects (in which case the implemented changes must be submitted afterwards as soon as possible).	or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, are substantial amendments and must be submitted to the relevant IECs and CAs (where applicable) for application for a favourable opinion/approval prior to being initiated, except when the changes are necessary to eliminate immediate hazards to the subjects (in which case the implemented changes must be submitted afterwards as soon as possible).	*which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety* ***or rights*** *of the subjects or on the reliability and robustness of the data generated in the clinical trial;" the* wording in the respective section of the CSP had to be adjusted.
A note regarding the rules for requesting substantial and non-substantial amendments/modifications to be followed by EU member states after transition of the trial to CTR has been		[..]	[..] The following phrase has been added: **Of note: For EU Member States, the above applies until having received authorisation for the transitioned trial via Clinical**	To ensure that the rules for requesting substantial and non-substantial modifications according to Chapter III, Article 15 of the CTR (*"A substantial modification, including the addition of a clinical trial*

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implemented.			**Trial Information System (CTIS). After authorisation of the transitioned trial in CTIS, clinical trials in EU member states will have to comply with the rules for requesting substantial and non-substantial modifications of the Regulation (EU) No. 536/2014.**	*site or the change of a principal investigator in the clinical trial site, may only be implemented if it has been approved in accordance with the procedure set out in this Chapter.")* are complied with after the transition of this clinical trial to CTR, a corresponding note has been added.
The reference to the CTR, which will be valid in all participating EU member states after the transition of this clinical trial, has been updated.	Section 12.1 – Trial Management and Monitoring	[..] The ICH GCP and the Directive 2001/20/EC of April 4, 2001 (or when it becomes applicable: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC), are intended to improve the quality of the various steps and activities in	[..] The ICH GCP and the Directive 2001/20/EC of April 4, 2001 (or ~~when it becomes applicable~~**following the transition of the trial**: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC), are intended to	To emphasize the applicability of the CTR after the transition of the clinical trial, it was necessary to adapt the associated references to the CTR.

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		the conduct of a clinical trial. The responsibilities of the sponsor, monitors, and investigators are regulated in this directive. The sponsor is obliged to set up a system to guarantee quality control at every stage in the conduct of the clinical trial.	improve the quality of the various steps and activities in the conduct of a clinical trial. The responsibilities of the sponsor, monitors, and investigators are regulated in this directive **(or following the transition of the trial in the CTR)**. The sponsor is obliged to set up a system to guarantee quality control at every stage in the conduct of the clinical trial.	
	Section 14.2 – Other Legal Bases	[..] • Directive 2001/20/EC (April 4, 2001), or when it becomes applicable: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC	[..] • Directive 2001/20/EC (April 4, 2001), or ~~when it becomes applicable~~ **following the transition of the trial**: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing	

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			Directive 2001/20/EC)	
This new section has been implemented to specify definition of 'Serious Breaches' and reporting requirements to be followed by EU member states after transition of the trial to CTR.	*New* Section 12.4 – Serious breaches	N/A	**12.4 Serious Breaches** **With the transition to Clinical Trials Regulation (EU) 536/2014 (Annex III, section 2.1 (2)), any deviation of the approved protocol version or the CTR that is likely to affect the safety, rights of trial subjects and/or data reliability and robustness to a significant degree in the clinical trial will be classified as a serious breach (for EU member states). Serious breaches will be reported to Dr. Falk Pharma GmbH by sites or vendors via the following email address:** PPD **and reported according to CTR (Regulation (EU) No. 536/2014). In parallel, the lead CRO will be informed**	To meet the requirements of the CTR concerning Article 52 ("The sponsor shall notify the Member States concerned of a serious breach of this Regulation or of the version of the Protocol in force at the time of the breach through the EU portal without undue delay and no later than seven days after becoming aware of the breach"), it became necessary to include a new section in the Protocol defining serious breaches and describing their handling.

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			by sites or vendor staff via the following e-mail address: [redacted] **The initial notification should include all available information on the suspected serious breach, and it should indicate the serious breach reporting deadline (i.e., not later than seven days of becoming aware of that breach). Additional information will be provided promptly to Falk Pharma GmbH and the lead CRO when it becomes available.** **Of note: For participating countries outside of the EU reporting requirements for serious breaches might differ from the ones mentioned above (local requirements of the respective country should be respected).**	

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To comply with CTR, the instructions for archiving period have been adjusted.	Section 15.2 15.2.1 – Investigator 15.2.2 – Sponsor	The investigator has to maintain a filing system for all documents relevant to the trial, such as the CD/DVDs of the eCRFs, the written informed consents, paper copies of questionnaires, the patient identification list, the patient records with the original data, drug dispensing log, and the investigator's trial file for a minimum of 15 years, [..] All printouts and electronic files of the eCRF data and all other documentation pertaining to the trial will be kept by Dr. Falk Pharma GmbH for a minimum of 15 years; [..]	The investigator has to maintain a filing system for all documents relevant to the trial, such as the CD/DVDs of the eCRFs, the written informed consents, paper copies of questionnaires, the patient identification list, the patient records with the original data, drug dispensing log, and the investigator's trial file for a minimum of ~~15~~**25** years, [..] All printouts and electronic files of the eCRF data and all other documentation pertaining to the trial will be kept by Dr. Falk Pharma GmbH for a minimum of ~~15~~**25** years, [..]	According to CTR (Article 58): *'Unless other Union law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law.'*
Heading and wording of section 19 was adapted/extended by information about submission of a summary of results, accompanied by	Section 19 – Summary of the results, final report and publication	N/A	**Beside the fully integrated CSR a summary of the results of the clinical trial as well as a summary for laypersons will be submitted to the MSCs within one year**	Heading and wording of section 19 was adapted/extended according to CTR (Article 37 (4)): *Irrespective of the outcome of a clinical trial, within one*

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a summary written in a language that is understandable for laypersons, to be prepared within one year from the end of the trial.			**after the end of the trial in the EU in accordance with the CTR (Regulation (EU) No. 536/2014). If the end of trial globally (EU and non-EU) should be later than the end of trial in the EU, the summary might be delivered later than within one year following end of trial in the EU, but as soon as possible, in order to include all data collected globally to ensure relevance of the statistical analysis.**	*year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. [..] It shall be accompanied by a summary written in a manner that is understandable to laypersons. [..]*

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In addition to the above-mentioned changes to the protocol further changes have been implemented with this Clinical Trial Protocol Version 2.0 / 21.12.2023 that became necessary with the altered COVID-19 Disease 2019 situation since pandemic status ended and became endemic in spring 2023. Furthermore, changes became necessary for logistical/administrative reasons, to harmonize the protocol with several updates performed for data recording in the eCRF and in order to remove several inconsistencies and/or imprecision and therefore to clarify the intent of the original Clinical Trial Protocol version 1.0, dated 25.03.2022. Finally two more endpoints have been added to get further insight regarding the contribution of different symptoms, especially nausea and bloating to the overall disease severity (and to account for the use of rescue medication.

Based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent Regulation (EU) No. 526/2014, these additional changes are considered to be substantial (e.g., changes of inclusion/exclusion criteria, supplementation of a further secondary endpoint) as well as non-substantial (further changes do neither significantly impacts the safety, rights or physical/mental integrity of subjects nor the scientific value of the trial).

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Inclusion criterion 11 was supplemented by a note specifying the use of hormonal contraceptives.	Synopsis - Inclusion Criteria and Section 3.1.1 – Inclusion Criteria	**11.** Women of childbearing potential agree to use a highly effective method of birth control, [..]	**11.** Women of childbearing potential agree to use a highly effective method of birth control, [..] **<u>Note:</u> Oral hormonal contraceptive methods should be supplemented by additional use of a male condom, as the trial drug might theoretically decrease the efficacy of some hormonal contraceptive methods.**	IC 11 was supplemented for reasons of specification and harmonisation (to be in line with wording of protocol section 6.4.5 *Pregnancy Test*).

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As a consequence of supplementation of inclusion criterion 11 wording was slightly modified/refined.	Section 6.4.5 – Pregnancy Testing	As the trial drug might theoretically decrease the effect of some hormonal contraceptive methods, all hormonal contraceptive methods should be supplemented by additional use of a male condom.	As the trial drug might theoretically decrease the ~~effect~~ **efficacy** of some hormonal contraceptive methods, **oral**~~all~~ hormonal contraceptive methods should be supplemented by additional use of a male condom.	Wording was modified to be consistent with changes/supplementation of Inclusion criterion 11.
Exclusion criterion 2 was supplemented.	Synopsis – Exclusion Criteria and Section 3.1.2 – Exclusion Criteria	2. History of major gastrointestinal surgery such as gastric bypass, anti-reflux surgery, gastric per oral endoscopic myotomy (G-POEM), gastrointestinal malignancy, colectomy (haemorrhoid surgery, appendectomy or cholecystectomy are permitted),	2. History of major gastrointestinal surgery such as gastric bypass, anti-reflux surgery, gastric per oral endoscopic myotomy (G-POEM), gastrointestinal malignancy, colectomy (haemorrhoid surgery, appendectomy or cholecystectomy**, and pyloric endoscopic dilation [if conducted more than 3 months prior to BSL (visit 2) and with a diameter of dilation ≤ 20 mm]** are permitted),	Former wording of EC 2 was supplemented to clarify that the surgical measure of pyloric dilatation is permitted under certain definitions.

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Exclusion criterion 4 was supplemented.	Synopsis - Exclusion Criteria and Section 3.1.2 – Exclusion Criteria	4. Gastric stimulator implant,	**4. Active** ~~**G**~~**g**astric stimulator implant,	Former wording was supplemented to emphasize that only patients with *active* gastric stimulator implants are to be excluded, not patients with implants in general.
Addition of systemic/oral anticholinergics to exclusion criterion 18 and slight modification of wording related to a potential extension of the screening phase	Synopsis - Exclusion Criteria and Section 3.1.2 – Exclusion Criteria	18. Any treatment within 2 weeks prior to BSL (visit 2) with medication that may alter gastrointestinal motility due to prokinetic/antiemetic effects: • Macrolide antibiotics (e.g., erythromycin), anti-malarials, anti-protozoals, anthelminthics, • Antidiarrheals and antispasmotics (e.g., butylscoplomaine), laxatives, • Opioids or cannabinoids,	18. Any treatment within **three days prior to the screening GEBT and** 2 weeks prior to BSL (visit 2) with medication that may alter gastrointestinal motility due to prokinetic/ **inhibiting**/antiemetic effects: • Macrolide antibiotics (e.g., erythromycin), anti-malarials, anti-protozoals, anthelminthics, • Antidiarrheals and antispasmotics (e.g., butylscoplomaine),	Systemic/oral anticholinergics have been added due to their potential to slower gastrointestinal motility (acting spasmolytic/relaxing on smooth muscles). *Inhibiting* effects have been added for further clarification of the exclusion criterion, since antidiarrheals, opiods, and systemic/oral anticholinergics show an inhibitory effect on gastrointestinal motility and

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		• Dopamine antagonists (e.g., metoclopramide, domperidone, alizapride), • 5-HT4 agonists (e.g., tegaserod, prucalopride), • 5-HT3 antagonists (e.g., tropisetron, ondansetron), • Anorectics (e.g., fenfluramine), • Other: aprepitant, lubiprostone, scopolamine (e.g., transdermal plaster).	laxatives, • Opioids or cannabinoids, • Dopamine antagonists (e.g., metoclopramide, domperidone, alizapride), • 5-HT4 agonists (e.g., tegaserod, prucalopride), • 5-HT3 antagonists (e.g., tropisetron, ondansetron), • Anorectics (e.g., fenfluramine), • **Systemic/oral anticholinergics (e.g., solifenacin, mebeverine); Exception: Inhaled parasympatholytics (e.g., ipratropiumbromide for COPD/Asthma) are allowed if used at standard stable doses,** • Other: aprepitant, lubiprostone, scopolamine (e.g., transdermal plaster).	therefore may trigger constipation. *'Within three days prior to the screening GEBT and'* has been added due to potential extension of screening period to 28 days between SCR 2 (visit 1) and BSL (visit 2).

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Exclusion criterion 21 has been supplemented by permission for the occasional use of local anesthetics for infiltration anaesthesia.	Synopsis – Exclusion Criteria and Section 3.1.2 – Exclusion Criteria	21. Class I and class III antiarrhythmics (e.g., propafenone, amiodarone) within 4 weeks prior to BSL (visit 2),	21. Class I and class III antiarrhythmics (e.g., propafenone, amiodarone) within 4 weeks prior to BSL (visit 2). **Occasional use of local anaethetics for infiltration anaesthesia is allowed (e.g. articaine, lidocaine),**	Even though local anaesthetics belong to class I antiarrhythmics, the sporadic use of local anaesthetics for infiltration anaesthesia during the trial has now been allowed, to facilitate the recruitment and to avoid protocol deviations. This is regarded as justified due to the fact that no pharmacodynamic interaction is expected, as local anaesthetics are not administered systemically. Therefore, patient safety will not be jeopardized by the occasional use of a local anesthetic (e.g. during dental procedures).

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Rephrasing of exclusion criterion 26 for clarity reasons	Synopsis – Exclusion Criteria and Section 3.1.2 – Exclusion Criteria	26. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: serotonin reuptake inhibitors, H2R antagonists, PPIs, calcium channel blockers, tricyclic antidepressants (in excess of 75 mg daily) and tetracyclic antidepressants,	26. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: serotonin reuptake inhibitors, H2R antagonists, PPIs, calcium channel blockers, tricyclic antidepressants (~~in excess of~~ **daily intake of up to** 75 mg **allowed**~~daily~~) and tetracyclic antidepressants,	To clarify that the ’75 mg’ does not refer to the 'dose change', but to the actual maximum daily dose.
Extension of number of trial sites and participating countries	Synopsis – Trial population	Approximately 320 adult male and female participants who have been diagnosed with gastroparesis (idiopathic or diabetic) will be recruited by trial sites located in Europe.	Approximately 320 adult male and female participants who have been diagnosed with gastroparesis (idiopathic or diabetic) will be recruited by trial sites located in ~~Europe~~**several European and non-European countries.**	Number of trial sites was increased, and participating countries were extended to non-European countries to support and accelerate recruitment of the trial.

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	Synopsis – Number of trial sites	Approximately 50 trial sites in several countries in Europe	Approximately ~~50~~**100** trial sites in **several European and non-European countries** ~~countries in Europe~~ **(e.g., in North America and Australia)**.	
	Section 3.2 – Trial Sites	It is intended that the trial will take place at approximately 50 trial sites in several countries in Europe specialized in gastroenterology and/or diabetology, at hospitals or private practices.	It is intended that the trial will take place at approximately ~~50~~**100** trial sites in several **European and non-European countries (e.g. in North America and Australia)** countries ~~in Europe~~ specialized in gastroenterology and/or diabetology, at hospitals or private practices.	
The IND number has been supplemented.	Header Title page Synopsis Signature pages	N/A	IND No: 169456	For the planned Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) it became necessary to add the corresponding IND number.

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Wording regarding guidelines and legislation associated with the ICF was generalised.	Section 6.4.6.2 – Sampling for Future Trial-Related Scientific Investigations - Optional	By informed consent, Patients will be informed about all relevant issues important to the patient as per GCP Guidelines and relevant European legislation.	By informed consent**, if applicable, p**atients will be informed about all relevant issues important to the patient as per GCP Guidelines and relevant ~~European~~ **national** legislation.	Wording regarding guidelines and legislation was generalised to be applicable in European and non-European countries. As optional blood sampling may not be performed in any of the participating countries, "if applicable" was added.
Availability of approved treatment of patients with gastroparesis in the U.S was added.	Section 1.1 – Disease Background	[..] Currently, there is no approved drug in Europe for the treatment of patients with gastroparesis.	[..] Currently, there is no approved drug in Europe for the treatment of patients with gastroparesis. **In the United States, metoclopramide is approved for diabetic gastroparesis, but the U.S. Department of Health and Human Services Food and Drug Administration (FDA) issued a black box warning against its permanent use (> 12 weeks).**	The availability of approved treatment of patients with gastroparesis in the U.S. was added, as participating countries were extended to non-European countries (e.g., U.S. and Australia).

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
	Section 1.3 – Rationale of the Trial	Currently, there is no approved drug for the treatment of patients with gastroparesis in Europe.	Currently, there is no approved drug for the treatment of patients with gastroparesis in Europe. **In the United States, metoclopramide is approved for diabetic gastroparesis, but the FDA issued a black box warning against its permanent use (> 12 weeks).**	
Correction of dose regimens used in former trial and specification of dose regimens in the current trial.	Section 1.3 – Rationale of the Trial	Naronapride efficacy and safety in patients with chronic idiopathic constipation were assessed in a previous clinical study administrating 20 mg, 40 mg (20 mg BID [twice daily]), 80 mg (40 mg BID) and 120 mg (40 mg TID) daily over 4 weeks. The 80 mg group showed the most consistently significant primary and secondary endpoint in this study. Though most common AEs including abdominal pain and headache appeared to be most frequent in patients who	Naronapride efficacy and safety in patients with chronic idiopathic constipation were assessed in a previous clinical study administrating 20 mg **BID (twice daily)**, 40 mg **BID** ~~(20 mg BID [twice daily])~~, 80 mg ~~(40 mg~~ BID~~)~~ and 120 mg **BID** ~~(40 mg TID)~~ daily over 4 weeks. The 80 mg **BID** group ~~showed~~ had the most consistently significant primary and secondary **efficacy** endpoints ~~in this study~~. Though most common AEs including abdominal pain	Dose regimens used in former trial were corrected according to IB. Dose regimens in the current trial were specified for better understanding and readability.

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
		took the highest dose (120 mg) Naronapride was overall well-tolerated in this study. Based on the results, 3 Naronapride dose regimens will be compared to placebo in this study: 10 mg, 20 mg, and 40 mg TID.	and headache appeared to be most frequent in patients who took the highest dose (120 mg **BID),** naronapride was overall well-tolerated in this study. Based on the**se** results, 3 naronapride dose regimens will be compared to placebo in this study: 10 mg **TID**, 20 mg **TID**, and 40 mg TID.	
Wording of the section was supplemented in order to underline the rationale for dose selection.	Section 1.3 – Rationale of the Trial	[..] Dose selection for this clinical trial is based on the results of earlier studies. In one study in healthy, female volunteers, the optimal dose of Naronapride for promotion of gastric emptying was 20 mg TID. The lower doses studied (3 and 10 mg TID) did not demonstrate an effect on gastric emptying. Naronapride efficacy and safety in patients with chronic idiopathic constipation were assessed in a previous clinical	[..] **The mechanism of primary action of naronapride resembles the mechanism of action of cisapride. Naronapride was designed to minimize potential cardio-vascular risks to allow its permanent use in patients with gastroparesis.** Dose selection for this clinical trial is based on the results of earlier studies **with naronapride.**	To further underline the rationale of dose selection, key characteristics of naronapride were added.

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		study administrating 20 mg, 40 mg (20 mg BID [twice daily]), 80 mg (40 mg BID) and 120 mg (40 mg TID) daily over 4 weeks. The 80 mg group showed the most consistently significant primary and secondary endpoint in this study. Though most common AEs including abdominal pain and headache appeared to be most frequent in patients who took the highest dose (120 mg) Naronapride was overall well-tolerated in this study. Based on the results, 3 Naronapride dose regimens will be compared to placebo in this study: 10 mg, 20 mg, and 40 mg TID.	In one study in healthy, female volunteers, the optimal dose of naronapride for promotion of gastric emptying was 20 mg TID. The lower doses studied (3 and 10 mg TID) did not demonstrate an effect on gastric emptying. Naronapride efficacy and safety in patients with chronic idiopathic constipation were assessed in a previous clinical study administrating 20 mg **BID (twice daily)**, 40 mg **BID** ~~(20 mg BID [twice daily])~~, 80 mg ~~(40 mg~~ BID~~)~~ and 120 mg **BID** ~~(40 mg TID)~~ daily over 4 weeks. The 80 mg **BID** group ~~showed~~ had the most consistently significant primary and secondary **efficacy** endpoints ~~in this study~~. Though most common AEs including abdominal pain and headache appeared to be most frequent in patients who	

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			took the highest dose (120 mg **BID),** naronapride was overall well-tolerated in this study. Based on the**se** results, 3 naronapride dose regimens will be compared to placebo in this study: 10 mg **TID**, 20 mg **TID**, and 40 mg TID.	
Change of estimated end of trial.	Synopsis – Trial duration	Estimated end: 4th quarter 2024 (last patient last visit [LPLV])	Estimated end: 4~~th~~ **1st** quarter ~~2024~~**2025** (last patient last visit [LPLV])	As the planned start of the trial has been delayed, the expected end of the trial has now been adjusted accordingly.
Information about estimated completion date of the CSR was removed.	Synopsis – Trial duration and Section 3.4 – Project Time Schedule	The estimated completion date of the clinical study report (CSR): one year after the end of the trial.	~~The estimated completion date of the clinical study report (CSR): one year after the end of the trial.~~	In the synopsis the phrase has been removed as the end of trial duration is sufficiently described with LPLV. In section 3.4 the phrase was removed to avoid redundancy in the body text (information about estimated completion date of the CSR and a summary of the results

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				has been supplemented in section 19).
A further secondary efficacy endpoint was supplemented (composite ANMS GCSI-DD average weekly total symptom score)	Synopsis - Secondary efficacy endpoints and Section 9.1.2 – Secondary efficacy endpoints	• Change of the modified ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT/WD (V6). *The modified daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) plus the score value for bloating divided by 6.* [..]	• Change of the modified ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT/WD (V6). *The modified daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) plus the score value for bloating divided by 6.* • **Change of the composite ANMS GCSI-DD average weekly total symptom score from BSL (V2) to EOT/WD (V6).** ***The composite daily ANMS GCSI-DD total symptom score is the sum of the score values (0-4) of only 4 core symptom items (nausea,***	Since the symptoms "vomiting" and "bloating" may be associated with gastroparesis only rarely and therefore do not represent characteristic symptoms of the disease, a further secondary efficacy endpoint, the “composite ANMS GCSI-DD average weekly total symptom score”, has been introduced to exclude these symptoms.

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			early satiety, postprandial fullness, upper abdominal pain) divided by 4. [..]	
A further exploratory endpoint was supplemented (number of days with intake of rescue medication).	Section 9.1.3 – Exploratory Endpoints	• [..] CGI-C score at Day 15, 29, 57 and at EOT/WD (V6).	• [..] • CGI-C score at Day 15, 29, 57 and at EOT/WD (V6). • **Number of days with intake of rescue medication from BSL (V2) until EOT/WD (V6).**	The endpoint has been supplemented because of the updated definition of dimenhydrinate and cyclizine (and additionally meclozine) as rescue medication/AMP.
A tolerance limit has been added for the period of taking the IMP (or drinking a glass of water respectively) prior to the test meal for the GEBT	Synopsis and Section 4 – Trial Design	[redacted CCI] [..] Treatment with the IMP will end with taking the last dose 30 minutes prior to the test meal for the GEBT at the EOT/WD visit (V6). [..]	[redacted CCI]. [..] Treatment with the IMP will end with taking the last dose 30 minutes **(15-35 minutes are considered acceptable)** prior to the test meal for the GEBT at the EOT/WD visit (V6). [..]	To simplify the process for the patient and the site personnel (and as regarded not critical) a tolerance is granted for the period of taking the IMP (or drinking a glass of water).respectively) prior to the test meal for the GEBT.

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	Section 6.3.4 – Interim Visits (ITR 1 [V3] to ITR 3 [V5])	• Directions for stop of treatment (at ITR 3 [V5], only): Treatment with the IMP will end with taking the last dose 30 minutes prior to the test meal for the GEBT.	• Directions for stop of treatment (at ITR 3 [V5], only): Treatment with the IMP will end with taking the last dose 30 minutes **(15-35 minutes are considered acceptable)** prior to the test meal for the GEBT.	
	Section 6.3.5 – End of Treatment Visit/Withdrawal Visit (EOT/WD; V6)	• Gastric emptying breath test (GEBT) including the intake of last dose of IMP 30 minutes prior to the test meal, see section 6.4.7	• Gastric emptying breath test (GEBT) including the intake of last dose of IMP 30 minutes **(15-35 minutes are considered acceptable)** prior to the test meal, see section 6.4.7	

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	Section 6.4.7 – Gastric Emptying Breath Test (GEBT)	For the GEBT at EOT/WD (V6) the last dose of the IMP must be taken 30 minutes prior to the GEBT test meal with a glass of water (100 mL). To perform both tests under the same conditions, patients should also drink 100 mL of water 30 minutes before the GEBT test meal in SCR 2 (V1).	For the GEBT at EOT/WD (V6) the last dose of the IMP must be taken 30 minutes **(15-35 minutes are considered acceptable)** prior to the GEBT test meal with a glass of water (100 mL). To perform both tests under the same conditions, patients should also drink 100 mL of water 30 minutes **(15-35 minutes are considered acceptable)** before the GEBT test meal in SCR 2 (V1).	
Screening phase was extended up to 6 weeks (period between SCR 2 visit 1) and BSL (visit 2) extended to 28 days)	Synopsis – Trial design	The overall trial duration for the individual participant is estimated to be approximately 20 weeks from screening to end of follow-up with maximum 8 visits. Screening Phase (Up to 4 Weeks): During the up to 4 weeks screening phase, the presence and persistence of trial-entry criteria will be evaluated.	The overall trial duration for the individual participant is estimated to be ~~approximately~~ ~~20~~**18-22** weeks from screening to end of follow-up with maximum 8 visits. Screening Phase (Up to ~~4~~**6** Weeks): During the ~~up to four~~**2 to 6** weeks lasting screening phase, the presence and persistence of trial-entry criteria will be	The flexible period between SCR 2 (visit 1) and BSL (visit 2) was extended to max. 28 days to ensure that test results of the GEBT are available at Baseline.

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			evaluated. [..] **The interval between SCR 2 (visit 1) and the baseline visit (BSL, visit 2) should be at least 2 weeks but may be extended up to 4 weeks to ensure that all screening results are available at the time of planned randomisation at BSL (visit 2).** From **SCR 2 (**visit **1)** onwards, [..]	
	Synopsis – Treatment duration	The treatment duration per participant is 12 weeks. The trial duration per participant is up to 20 weeks with a total of 8 trial visits: **Screening phase (SCR)**: Up to 4 weeks Visit 0: SCR 1 (Up to 14 days prior to SCR 2) Visit 1: SCR 2 (14 days prior to BSL (visit 2)	The treatment duration per participant is 12 weeks. The trial duration per participant is ~~up to~~ **18-22** weeks with a total of 8 trial visits: **Screening phase (SCR)**: Up to ~~4~~**6** weeks Visit 0: SCR 1 (Up to 14 days prior to SCR 2) Visit 1: SCR 2 (14 – **28** days prior to BSL (visit 2)	As a consequence, instructions for the GEBT (section 6.4.7) were modified, including the possibility to use the initial GEBT result in case a patient is re-screened (for the exceptional case that the GEBT-results are not available BSL - even after extended screening phase).

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<tr><td></td><td>Flow Chart</td><td>
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Visit Name</td><td>0
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SCR 2</td></tr>
<tr><td>Day</td><td>Up to 14 days prior to SCR 2</td><td>14 days prior to BSL(±2)</td></tr>
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<table>
<tr><th>ACTIVITIES</th><th colspan="2">TRIAL VISITS</th></tr>
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Visit Name</td><td>0
SCR 1</td><td>1
SCR 2</td></tr>
<tr><td>Day</td><td>Up to 14 days prior to SCR 2</td><td>14 – 28 days prior to BSL~~(±2)~~</td></tr>
</table>
</td><td></td></tr>
<tr><td></td><td>Section 3.4 – Project Time Schedule</td><td>Trial duration including screening, treatment and follow-up phase for each participant is approximately 20 weeks.</td><td>Trial duration including screening, treatment and follow-up phase for each participant is ~~approximately 20~~ 18-22 weeks.</td><td></td></tr>
<tr><td></td><td>Section 4 – Trial Design</td><td>The overall trial duration for the individual participant is estimated to be approximately 20 weeks from screening to end of follow-up with maximum 8 visits. The patients will be instructed to start the treatment with the IMP with the [redacted] at date of the BSL visit (V2, on day 1).</td><td>The overall trial duration for the individual participant is estimated to ~~be approximately 20~~18-22 weeks from screening to end of follow-up with maximum 8 visits. The patients will be instructed to start the treatment with the IMP with the [redacted] at date of the BSL visit (V2, on day 1).</td><td></td></tr>
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	Section 6.1 – Time Sequence and Frames	The trial period for an individual patient consists of an up to 4 weeks screening phase, a double-blind treatment phase of 12 weeks and a 4-week follow-up phase. Table 6-1: Visit Schedule **Day no**.: 14 days prior to BSL visit **Time window [days]:** ± 2	The trial period for an individual patient consists of an ~~up to 4~~ **2 to 6** weeks **lasting** screening phase, a double-blind treatment phase of 12 weeks and a 4-week follow-up phase. Table 6-1: Visit Schedule **Day no**.: 14 **- 28** days prior to BSL visit **Time window [days]:** ~~± 2~~
	Section 6.2 – Overview of Time Sequence	The trial will begin with a screening visit 1 (SCR 1; V0), which should take place within up to 28 days prior to the BSL visit (V2) or up to 14 days prior to the second SCR visit (SCR 2; V1), respectively. [,,] **Screening visit 2 (SCR 2; V1)** takes place 14 days before the BSL visit (V2).	The trial will begin with a screening visit 1 (SCR 1; V0), which should take place within up to ~~28~~**42**-days prior to the BSL visit (V2) or up to 14 days prior to the second SCR visit (SCR 2; V1), respectively. [..] **Screening visit 2 (SCR 2; V1)** takes place 14 **– 28** days before the BSL visit (V2).

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	Section 6.4.7 – Gastric Emptying Breath Test (GEBT)	During this study two GEBTs will be performed, the first one at SCR 2 (V1) and the second one at EOT/WD (V6). [..]	During this study two GEBTs will be performed, the first one at SCR 2 (V1) and the second one at EOT/WD (V6). **The GEBT at SCR 2 (V1) should be carried out at least 14 days prior to the planned BSL (V2).** **Please note that patients taking any medications known to influence the rate of gastric emptying (as detailed in exclusion criterion 18) need to discontinue these medications within three days prior to the screening GEBT.** **In the exceptional case that the results of the screening GEBT are not available at the time of the scheduled BSL (V2), the period until BSL (V2) may be extended to a maximum of 28 days.**	

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			If GEBT results are not available at the end of the screening period, a patient may be re-screened. Prior to a re-screening it should be discussed with the Sponsor and/or the MM whether the results of GEBT from the initial screening can still be used or if there is the need to repeat the GEBT as part of the re-screening procedures. [..]	
		Note: The following has to be taken into account: [..] Patients taking any medications known to influence the rate of gastric emptying (e.g., erythromycin, metoclopramide, opiates, and anticholinergics) need to discontinue these medications within three days prior to the screening GEBT.	Note: The following has to be taken into account: [..] ~~Patients taking any medications known to influence the rate of gastric emptying (e.g., erythromycin, metoclopramide, opiates, and anticholinergics) need to discontinue these medications within three days prior to the screening GEBT.~~	

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The period for the allowed use of rescue medication (*if not applied for more than 2 days per week*) has been adjusted.	Synopsis – Exclusion criteria and Section 3.1.2 – Exclusion Criteria	19. H1-receptor antihistamines of first generation (e.g., doxylamine) within 2 weeks prior to BSL (visit 2) Note: dimenhydrinate (cyclizine in the Netherlands, only) in the standard daily prescribed dose is allowed if not applied for more than 2 days per week in the two weeks prior to BSL (visit 2),	19. H1-receptor antihistamines of first generation (e.g., doxylamine) within 2 weeks prior to BSL (visit 2) ~~Note~~**Exception**: **Locally sourced OTC preparations against nausea (preferably** dimenhydrinate, **alternatively** cyclizine **or meclozine**~~in the Netherlands, only~~) **as rescue medication** in the standard daily prescribed dose ~~is~~ **are** allowed if not applied for more than 2 days per week ~~in the two weeks prior to BSL (V2)~~ **from SCR 2 (V1) onwards**	Due to the possible extension of the screening period between screening visit 2 and baseline visit to max. 28 days, the period for the allowed use of dimenhydrinate and cyclizine (and additionally meclozine) has been adjusted.

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	Section 6.4.12.6 – Daily Diary for Intake of Rescue Medication (if applicable)	As described in section 5.6 participants are allowed to use dimenhydrinate or cylizine in the standard prescribed dose to reduce their disease symptoms if necessary, provided that dimenhydrinate or cyclizine is not applied for more than 2 days per week in the two weeks prior to BSL (V2) and during the DBT phase until EOT/WD (V6).	As described in section 5.6.**2** participants are allowed to use dimenhydrinate ~~**or**~~ **(alternatively** cy**c**lizine **or meclozine)** in the standard prescribed dose to reduce their disease symptoms if necessary, provided that dimenhydrinate/~~**or**~~ cyclizine/**meclozine** is not applied for more than 2 days per week ~~in the two weeks prior to BSL (V2)~~ **from SCR 2 (V1) onwards** and during the DBT phase until EOT/WD (V6).	
Sites are allowed to combine the first screening visit (SCR 1, V0) and the second screening visit (SCR 2, V1) to one single visit.	Synopsis – Trial design	Screening Phase Apart from one Quality of Life questionnaire, an electronic tool (ePROM) will be used in this trial for documentation of Patient Reported Outcomes Measures. [..]	Screening Phase Apart from one Quality of Life questionnaire, an electronic tool (ePROM) will be used in this trial for documentation of Patient Reported Outcomes Measures. **It will be allowed to combine the first screening visit (SCR 1, visit**	By allowing the site personnel to combine SCR1 and SCR2 the clinical trial sequence is refined and simplified for the patient.

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<tr><td></td><td>Flow Chart</td><td><table><tr><th colspan="3">TRIAL VISITS</th></tr><tr><th>Screening (SCR)</th><th>Double-blind Treatment (DBT)</th><th>Follow-Up (FU)</th></tr></table></td><td>0) and the second screening visit (SCR 2, visit 1) in one single visit, provided that all assessments required for SCR 1 and SCR 2 can be performed at the same day.
[..]
<table><tr><th colspan="3">TRIAL VISITS</th></tr><tr><th>Screening (SCR)*</th><th>Double-blind Treatment (DBT)</th><th>Follow-Up (FU)</th></tr></table>
* If it is possible to perform all required screening assessments on the same day, SCR 1 and SCR 2 can be combined as one visit. In this case, assessments scheduled for both visits do not have to be performed twice.
[..]
1 ~~For female participants of childbearing potential~~ Urine test at SCR 1 (V0), ~~serum human chorionic gonadotropin (hCG) test at SCR 2 (V1), urine~~ at BSL (V2), all ITRs (V3 to V5), EOT/WD (V6), and FU/EOS (V7) to be performed for female patients of child-bearing potential.
Serum human chorionic gonadotropin (hCG) test at SCR 2 (V1) will be performed for all female patients below age of 60.</td><td></td></tr>
</table>

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
			Note: In case SRC 1 and SRC 2 will be combined as one visit a serum pregnancy test should be performed that visit.	
	Section 6.1 – Time Sequence and Frames	Table 6-1: Visit Schedule Footnote 1) Randomisation is performed centrally via IRT.	Table 6-1: Visit Schedule Footnote **1) If it is possible to perform all required screening assessments on the same day, SCR 1 and SCR 2 can be combined as one visit. In this case, assessments scheduled for both visits do not have to be performed twice.** **2) The interval between SCR 2 and BSL visit should be at least 2 weeks but may be extended up to 4 weeks to ensure that all screening results are available at the time of planned randomisation at BSL visit.** **3)** Randomisation is performed centrally via IRT.	
	Section 6.2 – Overview of Time Sequence	The trial will begin with a **screening visit 1 (SCR 1; V0)**, which should take place within up to 28 days prior to the BSL visit (V2) or up to 14 days	The trial will begin with a **screening visit 1 (SCR 1; V0)**, which should take place within up to ~~28~~**42**-days prior to the BSL visit (V2) or up to 14	

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		prior to the second SCR visit (SCR 2; V1), respectively.	days prior to the second SCR visit (SCR 2; V1), respectively.	
		Patients who are interested in participating in the trial will be asked by the investigator after a conscientious explanation, to sign an informed consent prior to any trial-specific procedures or examinations (see section 13.1).	**However, both visits, i.e., SCR 1 visit (V0) and SCR 2 visit (V1) might be combined to one visit only, in case that it will be possible to perform all necessary screening assessments in one day only.** Patients who are interested in participating in the trial will be asked by the investigator after a conscientious explanation, to sign an informed consent prior to any trial-specific procedures or examinations (see section 13.1).	
	Section 6.3.1 – Screening Visit 1 (SCR 1; V0)	[..] Urine human chorionic gonadotropin (hCG) pregnancy test (only in female participants of childbearing potential), see section 6.4.5.	[..] Urine human chorionic gonadotropin (hCG) pregnancy test (only in female participants of childbearing potential), see section 6.4.5. **In**	

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			case SCR 1 and SCR 2 will be combined to one visit on the same day, a serum hCG pregnancy should be performed.	
	Section 6.4.5 – Pregnancy Test	Female patients of childbearing potential are only eligible for the trial in case of a negative pregnancy test result during screening (SCR 1 [V0]: urine pregnancy test and SCR 2 [V1]: serum pregnancy test) and at BSL (V2) visit (urine pregnancy test).	Female patients of childbearing potential are only eligible for the trial in case of a negative pregnancy test result during screening (SCR 1 [V0]: urine pregnancy test and SCR 2 [V1]: serum pregnancy test) and at BSL (V2) visit (urine pregnancy test). **Note: In case SRC 1 and SRC 2 will be combined as one visit a serum pregnancy test should be performed that visit.**	
Instructions for female patients and serum pregnancy testing have been corrected and specified in section 6.4.5.	Synopsis - Inclusion Criteria and	[..] Women of non-childbearing potential (surgically sterile [e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy], or	[..] Women of non-childbearing potential (surgically sterile [~~e.g.,~~**i.e.,** hysterectomy, bilateral salpingectomy, bilateral oophorectomy], or	Wording was adjusted for the following reasons: • The definition for surgically sterile women was specified by limitation to the named surgeries.

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	Section 3.1.1 – Inclusion Criteria Section 6.4.5 – Pregnancy Test	postmenopausal with at least two years without spontaneous menses) may be included. [..] Following information has to be collected for female patients: • Surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy), • Postmenopausal for at least 2 years (i.e., no menses for at least 2 years without an alternative medical cause), or • Childbearing potential. From BSL (V2) ongoing, urine hCG pregnancy tests for female patients of childbearing potential will be repeated at each visit including the follow-up (EOS/FU, V7). In case the serum pregnancy test result for surgically sterile female subjects or female subjects of	postmenopausal with at least two years without spontaneous menses) may be included. [..] Following information has to be collected for female patients: • Surgically sterile (~~e.g.~~**i.e.**, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), • Postmenopausal for at least 2 years (i.e., no menses for at least 2 years without an alternative medical cause), or • Childbearing potential. ~~From BSL (V2) ongoing, urine hCG pregnancy tests for female patients of childbearing potential will be repeated at each visit including the follow-up (EOS/FU, V7).~~ **At SCR 2, a serum hCG pregnancy test will be performed as part of the central laboratory**	• In the original Clinical Trial Protocol, version 1.0, it was stated by mistake that urine hCG pregnancy tests will be performed for female patients of childbearing potential only; however, the central lab of the trial is routinely performing serum hCG pregnancy tests for all women below age of 60. In the original Clinical Trial Protocol, version 1.0, it was stated by mistake that a serum pregnancy test with a result "uncertain" has to be repeated for surgically sterile female subjects or female subjects of childbearing potential; however, a re-test is only required and performed for women of childbearing potential.

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		childbearing potential is "uncertain", the serum pregnancy re-test must be performed. Serum pregnancy test with a result "uncertain" is only acceptable when a subject is post-menopausal since at least 2 years.	**assessment for all female patients below age of 60.** In case the serum pregnancy test result ~~for surgically sterile female subjects or~~ for female subjects of childbearing potential is "uncertain", the serum pregnancy re-test must be performed. Serum pregnancy test with a result "uncertain" is ~~only~~ acceptable when a subject is **surgically sterile or** post-menopausal since at least 2 years. **From BSL (V2) ongoing, urine hCG pregnancy tests for female patients of childbearing potential will be repeated at each visit including the follow-up (EOS/FU, V7).**	

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	Flow Chart	Footnote 1 1 For female participants of child-bearing potential: urine test at SCR 1 (V0), serum human chorionic gonadotropin (hCG) test at SCR 2 (V1), urine test at BSL (V2), all ITRs (V3 to V5), EOT/WD (V6) and FU/EOS (V7).	Footnote 1 1 ~~For female participants of childbearing potential~~ **Urine test** at SCR 1 (V0), ~~serum human chorionic gonadotropin (hCG) test at SCR 2 (V1), urine~~ at BSL (V2), all ITRs (V3 to V5), EOT/WD (V6), and FU/EOS (V7) **to be performed for female patients of child-bearing potential.** **Serum human chorionic gonadotropin (hCG) test at SCR 2 (V1) will be performed for all female patients below age of 60.** **Note: In case SRC 1 and SRC 2 will be combined as one visit a serum pregnancy test should be performed that visit.**	
	Section 6.3.2 – Screening Visit 2 (SCR 2; V1)	**Examinations** [..] Serum hCG pregnancy test (only for females of childbearing potential, see section 6.4.5)	**Examinations** [..] Serum hCG pregnancy test (~~only~~ **for all females patients below age of 60**~~of childbearing potential~~, see section 6.4.5)	

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	Section 6.4.6.1 – Safety Assessments	All other parameters will be analysed in the central laboratory: [..] Serum chemistry: [..] At SCR 2 (V1) only: Serum hCG for female patients of childbearing potential.	All other parameters will be analysed in the central laboratory: [..] Serum chemistry: [..] At SCR 2 (V1) only: Serum hCG for **all** female patients **below age of 60**~~**of childbearing potential**~~.	
Instructions for reporting and follow-up of pregnancies have been adjusted.	Section 7.1.2 – Serious Adverse Events Section 7.1.4 – Pregnancies	If unintended pregnancy occurs during the course of the trial, pregnancy [..] If any female patient is found to be pregnant during the screening period, the treatment period of the trial (in which case IMP must be stopped immediately) or within 28 days of last dose of IMP, the investigator must discuss with the patient further treatment management. Patients who	If unintended pregnancy occurs **between the first administration of the IMP (V2) and up to 28 days of last dose of IMP**, pregnancy [..] If any female patient is found to be pregnant during the treatment period of the trial (in which case IMP must be stopped immediately) or within 28 days of last dose of IMP, the investigator must discuss with the patient further treatment management. Patients who become pregnant	In the original Clinical Trial Protocol, version 1.0, it was stated that unintended pregnancies *occurring from screening period onwards* should be reported in the same way as an SAE (and per pregnancy form in addition) and should be followed up as per protocol for safety reasons (sections 7.1.2 and 7.1.4). However, for reasons of harmonisation with wording of the pregnancy ICF and current Standard Operating Procedures (SOPs) of Dr.

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		become pregnant between the first screening visit (V0) up to 28 days after the last administration of the IMP will be followed up as per protocol for safety reasons. Pregnancy occurring between the first screening visit (V0) and up to 28 days of last dose of IMP has to be documented as an AE and to be reported in the same way as an SAE (using the SAE form, see section 7.2.2), [..]	**after the first administration of the IMP and** up to 28 days after the last administration of the IMP will be followed up as per protocol for safety reasons. Pregnancy occurring between the first screening visit (V0) and up to 28 days of last dose of IMP has to be documented as an AE**. Pregnancy occurring after the first administration of the IMP and up to 28 days of last dose of IMP** ~~and~~ **has** to be reported in the same way as an SAE (using the SAE form, see section 7.2.2), [..]	Falk Pharma GmbH, instructions have been adjusted, i.e., only pregnancies occurring *after the first administration of the IMP* (and up to 28 days of last dose of IMP) should be reported in the same way as an SAE (and per pregnancy form in addition) and be followed up as per protocol for safety reasons.

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<table>
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(CSP v2.0 / 21.12.2023)</th><th>Rationale</th></tr>
<tr>
<td>Deletion of COVID-19 procedures/provisions</td>
<td>Flow Chart</td>
<td>
<table>
<tr><th></th><th colspan="6">Only applies during COVID-19 Pandemic</th></tr>
<tr><td>Check for clinical signs and symptoms of COVID-19</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
<tr><td>SARS-CoV-2 RT-PCR Test[6]</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
</table>
[..] ECG = Electrocardiogram; SARs-CoV-2 = Severe acute respiratory syndrome coronavirus type 2; RT-PCR test = Real-time reverse transcriptase-polymerase chain reaction;[..]
6 SARS-CoV-2 RT-PCR test only applicable if COVID-19 clinical signs and symptoms are confirmed by the investigator or if a SARS-CoV-2 RT-PCR test (or antigen test) is required according to the usual routine at site.
</td>
<td>
<table>
<tr><th></th><th colspan="6">~~Only applies during COVID-19 Pandemic~~</th></tr>
<tr><td>~~Check for clinical signs and symptoms of COVID-19~~</td><td>~~●~~</td><td>~~●~~</td><td>~~●~~</td><td>~~●~~</td><td>~~●~~</td><td>~~●~~</td></tr>
<tr><td>~~SARS-CoV-2 RT-PCR Test~~[6]</td><td>~~●~~</td><td>~~●~~</td><td>~~●~~</td><td>~~●~~</td><td>~~●~~</td><td>~~●~~</td></tr>
</table>
[..] ECG = Electrocardiogram; ~~SARs-CoV-2 = Severe acute respiratory syndrome coronavirus type 2~~; RT-PCR test = Real-time reverse transcriptase-polymerase chain reaction;[..]
~~6 SARS-CoV-2 RT-PCR test only applicable if COVID-19 clinical signs and symptoms are confirmed by the investigator or if a SARS-CoV-2 RT-PCR test (or antigen test) is required according to the usual routine at site.~~
Includes renumbering of subsequent footnotes
</td>
<td>Pandemic status ended and became endemic in spring 2023.</td>
</tr>
</table>

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	Section 1.4 – Benefit/Risk Assessment	Participation in clinical trials may currently be associated with increased risks and challenges due to the Coronavirus Disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). [..] If additional mitigation measures require approval, a substantial amendment will be submitted to the relevant IEC and the CA and will not be implemented until approved, except in case of an immediate hazard.	~~Participation in clinical trials may currently be associated with increased risks and challenges due to the Coronavirus Disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2).~~ ~~[..]~~ ~~If additional mitigation measures require approval, a substantial amendment will be submitted to the relevant IEC and the CA and will not be implemented until approved, except in case of an immediate hazard.~~	
	Section 3.1 – Patient selection	*Applies only during the COVID-19 pandemic:* [..] If no SARS-CoV-2 infection is suspected, a patient can be invited to the SCR 1 (V0).	~~*Applies only during the COVID-19 pandemic:*~~ ~~[..]~~ ~~If no SARS-CoV-2 infection is suspected, a patient can be invited to the SCR 1 (V0).~~	

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	Section 6.1 – Time Sequence and Frames	Applies only during the COVID-19 pandemic: Possible deviations from the above-mentioned schedule, that may become necessary during escalating pandemic situation are summarized in an addendum to this Clinical Trial Protocol ("Mitigation Measures due to COVID-19 Pandemic").	~~Applies only during the COVID-19 pandemic:~~ ~~Possible deviations from the above-mentioned schedule, that may become necessary during escalating pandemic situation are summarized in an addendum to this Clinical Trial Protocol ("Mitigation Measures due to COVID-19 Pandemic").~~	
	Section 6.3 – Description of the Clinical Trial Sequence	*Applies only during the COVID-19 pandemic:* [..] Depending on the situation at the site, necessary assessments and examinations might be postponed until the test result is available.	~~*Applies only during the COVID-19 pandemic:*~~ ~~[..]~~ ~~Depending on the situation at the site, necessary assessments and examinations might be postponed until the test result is available.~~	

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	Section 6.3.1 – Screening Visit 1 (SCR1;V0) to Section 6.3.6 – End of Study Visit/Follow-Up Visit (EOS/FU;V7)	**Examinations** • Check for clinical signs and symptoms of COVID-19 (SARS-CoV-2 RT-PCR test only if clinically confirmed symptoms) [..]	**Examinations** • ~~Check for clinical signs and symptoms of COVID-19 (SARS-CoV-2 RT-PCR test only if clinically confirmed symptoms)~~ [..]	
	Section 8.1 – (Withdrawal) Criteria in Individual Cases	In general, withdrawn patients will not be replaced, except in case that patients are withdrawn due to restrictions which might occur in the context of the ongoing COVID-19 pandemic (e.g., in case the conduction of the clinical trial in a protocol-conformal manner is no longer possible due to a new pandemic situation comparable to the COVID-19 pandemic in spring 2020).	~~In general, withdrawn patients will not be replaced, except in case that patients are withdrawn due to restrictions which might occur in the context of the ongoing COVID-19 pandemic (e.g., in case the conduction of the clinical trial in a protocol-conformal manner is no longer possible due to a new pandemic situation comparable to the COVID-19 pandemic in spring 2020).~~	

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		[..] In case of a withdrawal, whenever possible, WD (V6) and FU Visit (V7) should be performed as planned for safety reasons, provided that the patient has recovered from COVID-19 by the time of the visit.	~~[..]~~ ~~In case of a withdrawal, whenever possible, WD (V6) and FU Visit (V7) should be performed as planned for safety reasons, provided that the patient has recovered from COVID-19 by the time of the visit.~~	
	Section 8.2.1 – Termination of the Whole Trial	*Applies only during the COVID-19 pandemic:* Recruitment at a single site or all participating sites in a single country can be stopped prematurely if further recruitment seems to be impossible until the end of the planned recruitment period due to escalating COVID-19 pandemic situation. If no further on-site visits can be performed, the investigator(s) must promptly inform the trial participants and assure appropriate therapy in	~~*Applies only during the COVID-19 pandemic:*~~ ~~Recruitment at a single site or all participating sites in a single country can be stopped prematurely if further recruitment seems to be impossible until the end of the planned recruitment period due to escalating COVID-19 pandemic situation. If no further on-site visits can be performed, the investigator(s) must promptly inform the trial participants and assure appropriate therapy in~~	

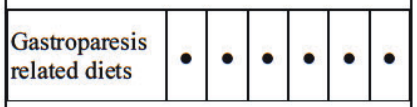
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		accordance with the standard of care.	~~accordance with the standard of care.~~	
	Section 12.3 – Risk Management	As local circumstances will possibly lead to a (temporary) local or general change in risk assessment with the escalation of the current pandemic COVID-19 situation, risk-management will include an investigator-driven risk assessment. [..] In this case the relevant IEC and the CA will be notified about changes as soon as possible considering national and local circumstances.	~~As local circumstances will possibly lead to a (temporary) local or general change in risk assessment with the escalation of the current pandemic COVID-19 situation, risk-management will include an investigator-driven risk assessment.~~ ~~[..]~~ ~~In this case the relevant IEC and the CA will be notified about changes as soon as possible considering national and local circumstances.~~ Includes removal of references.	

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The positions of Managing Director and Drug Safety Manager at the Sponsor have been refilled and the higher-level department has been renamed.	Signature Page	Managing Director (Medicine and Pharmacy)  Drug Safety Manager 	Managing Director (~~Medicine and Pharmacy~~ **Science and Innovation**)  Drug Safety Manager 	Change for administrative reasons.
Correction and harmonisation of wording.	Flow Chart	Footnote 7 7 Differential blood count only at SCR 2 (V1), BSL (V2) and EOT/WD (V6).	Footnote 7 7 Differential blood count only at ~~SCR 2 (V1),~~ BSL (V2) and EOT/WD (V6).	For harmonisation with wording in section 6.4.6.1 ([..] *including differential blood count (at BSL [V2] and EOT/WD [V6], only) [..])*.
Instructions for eating habits during the trial has been added.	Section 5.2 – Character-isation of IMP	Table 5-2: Characteristics of Naronapride placebo film-coated tablets [..]	Table 5-2: Characteristics of naronapride placebo film-coated tablets [..] **All trial participants are to be instructed to keep their normal eating habits during**	For clarity reasons, the instruction for patients to keep their normal eating habits during the clinical trial, as already stated in the synopsis, has now been included in section 5.2 of the

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			the trial and [redacted] CCI CCI	Clinical Trial Protocol in addition.
Insertion of a description for the documentation of dietary measures.	Flow Chart Section 6.4.2 – Case history / Medical history	N/A 6.4.2 Case history/Medical history [..] If any ongoing disease resolves during the course of the study the stop date should be provided.	 6.4.2 Case history/Medical history/**History of gastroparesis related diets** [..] If any ongoing disease resolves during the course of the study the stop date should be provided. **One aspect which may have an impact on symptoms experienced by the patient is related to his/her diet. Therefore, any special diet the patient is following due**	Usually, dietary measures are the first-line measures for gastroparesis. It was therefore considered necessary to also collect dietary measures in the context of the patient's case history. Since the documentation of dietary measures in the original Clinical Trial Protocol, version 1.0 was not sufficiently described, a corresponding description has now been added.

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			to gastroparesis for the last 3 months prior to BSL (V2) and up until end of the trial (EOS/FU, V7) must be recorded in the eCRF as well as in the patient's medical records. Documentation should include the following: • **The type of diet (e.g., low fat, low fiber, no dairy products)** • **The Start and stop date (if not ongoing at the time of last visit (EOS/FU, V7)** **Patients should be advised to report any changes in gastroparesis related diets during the course of the study to the investigator/site personnel.**	
	Section 15.1 - Direct Access to Source	At least the following data must be recorded in the patient's medical records or must be	At least the following data must be recorded in the patient's medical records or must be	

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	Documents According to ICH GCP	included in the patient's medical record: **[..]** • General medical history and concomitant diseases • Previous (over the last 3 months prior to BSL, V2) and concomitant medications [..]	included in the patient's medical record: **[..]** • General medical history and concomitant diseases • **Gastroparesis related diets (for the last 3 months prior to BSL (V2) and up until end of the trial [EOS/FU, V7])** • Previous (over the last 3 months prior to BSL, V2) and concomitant medications [..]	

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Time period for the documentation of clinical symptoms of gastroparesis has been adapted.	Section 6.4.2 – Case history / Medical history	[..] • Details of current and previously experienced clinical symptoms of idiopathic or diabetic gastroparesis: nausea, vomiting, early satiety, postprandial fullness, bloating, upper abdominal pain, or others [to be specified] (never, previous [only if currently not present], current ≤ 3 months; current > 3 months) [..]	[..] • Details of current and previously experienced clinical symptoms of idiopathic or diabetic gastroparesis **for at least 3 months leading up to BSL (V2)**: nausea, vomiting, early satiety, postprandial fullness, bloating, upper abdominal pain, or others [to be specified**] (yes/no)** ~~(never, previous [only if currently not present], current ≤ 3 months; current > 3 months)~~ [..]	The time period for the medical history documentation was adjusted in order to comply with: 1. Wording of inclusion criterion 4 2. An update performed for data recording in the eCRF.
Correction of wording regarding the handling of GEBT results	Section 6.4.7 – Gastric Emptying Breath Test (GEBT)	Printouts of the test results need to be stored in the patient's medical records and gastric emptying $T_{1/2}$ must be documented in the eCRF. In addition, further test results	Printouts of the test results need to be stored in the patient's medical records and gastric emptying $T_{1/2}$ must be documented in the eCRF. In addition, ~~further~~ **all** test results will be regularly transferred **to**	By mistake it was stated in the original Clinical Trial Protocol, version 1.0, that test results of the GEBT will be transferred to the eCRF. However, data from GEBT are not uploaded to the

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
		will be regularly transferred electronically in the eCRF.	**the DM for integration of respective data into the clinical data base** ~~electronically in the eCRF~~.	eCRF, but are transferred to the clinical database as an external data source.
Correction of total blood volume taken	Section 6.4.6 – Laboratory Parameters	For central and local laboratory assessments a total blood volume of approximately 145 mL is to be taken during the complete trial. If necessary, for safety reasons, additional blood samples may be taken.	For central and local laboratory assessments a total blood volume of approximately ~~145~~**90 to 100** mL is to be taken during the complete trial. If necessary, for safety reasons, additional blood samples may be taken.	Originally, further blood sampling was planned to be taken as part of this trial, but this was finally omitted. As a result, the total volume of blood drawn from a patient during the course of the trial reduced from 145 mL to only 90-100 mL, as correctly described in the ICF. For consistency reasons, this has now been corrected in the Clinical Trial Protocol.
Correction and harmonisation of wording.	Section 6.4.6.1 – Safety Assessments	(Fasting) glucose level – to be performed at dates of GEBT at SCR 2 (V1) and at EOT/WD (V6), for more details see section 6.4.7.	(Fasting) glucose level – to be performed ~~at dates of GEBT~~ at SCR 2 (V1) **for all patients**, and at BSL (V2) and at EOT/WD (V6) **for diabetics only**~~, for more details see section~~ 6.4.7.	By mistake it was stated in section 6.4.6.1 of the original Clinical Trial Protocol, version 1.0, that (fasting) glucose level will be determined at dates of GEBT for all patients.

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
				Correction was done as described to harmonize with the Flow Chart and Laboratory Manual.
Subdivision of former section 6.4.12.6 into two subsections	Section 6.4.12.6 – Daily Diary for Intake of Dimenhydrinate or Cyclizine [for the Netherlands, only] (if applicable) and Diary for Use of other Medication (not taken on a regular basis)	6.4.12.6 Daily Diary for Intake of Dimenhydrinate or Cyclizine [for the Netherlands, only] (if applicable) and Diary for Use of other Medication (not taken on a regular basis)	**6.4.12.6 Daily Diary for Intake of ~~Dimenhydrinate or Cyclizine [for the Netherlands, only] and Diary for Use of other Medication (not taken on a regular basis)~~ Rescue Medication (if applicable)** and **6.4.12.7 Diary for Use of other Medication (not taken on a regular basis)**	To improve clarity and readability previous section 6.4.12.6 has been divided into two subsections
Instructions for the investigator to transfer diary documentation of rescue medication intake to the eCRF have been deleted.	Section 6.4.12.7 – Diary for Use of other Medication	Based on the information as reported by patient, the investigator should document the use of dimenhydrinate or cyclizine and the use of other medication as concomitant	Based on the information as reported by patient, the investigator should document ~~**the use of dimenhydrinate or cyclizine and**~~ the use of other medication as concomitant	To avoid redundant documentation, instructions to transfer data for the use of rescue medication from the diary to the concomitant

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
	(not taken on a regular basis)	medication in the eCRF, providing the information as detailed in section 5.6.3	medication in the eCRF, providing the information as detailed in section 5.6.3.	medication module of the eCRF have been removed.
Correction of imprecision regarding the reporting of pregnancies	Section 7.1.2 – Serious Adverse Events	If unintended pregnancy occurs during the course of the trial, pregnancy will be regarded as an SAE.	If unintended pregnancy occurs during the course of the trial, pregnancy ~~will be regarded as an SAE~~ **has to be reported in the same timely way as an SAE**.	Wording was revised for better understanding with regard to reporting requirements of unintended pregnancy.
Clarification regarding the documentation of clinically abnormal findings prior to the first application of the IMP	Section 7.2 – AEs - Documentation and reporting	A condition (e.g., abnormal physical examination finding, abnormal laboratory finding, any symptom or disease) which is detected during screening phase (i.e., prior to the first administration of the IMP) and for which it is reasonable to assume that this condition already started prior to signing the ICF will be documented as concomitant disease in the 'Medical history and Concomitant Diseases' section of the eCRF.	A condition (e.g., abnormal physical examination finding, abnormal laboratory finding, any symptom or disease) which is detected during screening ~~phase (i.e., prior to the first administration of the IMP)~~**or baseline examination** and for which it is reasonable to assume that this condition already started prior to signing the ICF will be documented as concomitant disease in the 'Medical history and Concomitant Diseases' section of the eCRF.	To eliminate a discrepancy regarding the documentation of clinically abnormal findings in the screening phase including baseline, i.e. before the first application of IMP, harmonization in wording became necessary.

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Change	**CSP sections affected**	**Original Text (CSP v1.0 / 25.03.2022)**	**Revised Text (CSP v2.0 / 21.12.2023)**	**Rationale**
Options for AE documentation regarding 'Actions taken concerning trial medication' have been extended	Section 7.2.1 – Documentation and Reporting of Adverse Events	**Actions taken concerning trial medication** will be commented on as follows: 1) None, i.e., IMP was not changed, 2) IMP was withdrawn, Not applicable.	**Actions taken concerning trial medication** will be commented on as follows: 1) None, i.e., IMP was not changed, **2) IMP was interrupted** 3) IMP was withdrawn, Not applicable.	Addition of the option 'IMP was interrupted' became necessary to harmonize the protocol with an update performed for data recording in the eCRF for adequate AE documentation in case of a negative de-challenge.
Subdivision of former section 7.2.2 into two subsections	Section 7.2.2 – Documentation and Reporting of Serious Adverse Events	7.2.2 Documentation and Reporting of Serious Adverse Events	7.2.2 Documentation and Reporting of Serious Adverse Events **7.2.2.1 Investigator's Reporting Responsibilities for SAEs** [..] **7.2.2.2 Reporting Responsibilities of the Sponsor** [..]	The splitting into two subchapters was done to clarify SAE reporting responsibilities of both parties involved – the Investigator and the Sponsor.

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Change	**CSP sections affected**	**Original Text (CSP v1.0 / 25.03.2022)**	**Revised Text (CSP v2.0 / 21.12.2023)**	**Rationale**
The instructions for the process of unblinding for notification of a SUSAR have been specified/corrected.	Section 7.2.2 – Documentation and Reporting of Serious Adverse Events (new section 7.2.2.2 – Reporting Responsibili-ties of the Sponsor)	Since the definition of every SUSAR requires knowledge of the precise investigational product used, unblinding will be carried out by named staff of the sponsor responsible for drug safety. Only two members of the company staff (DSM or deputy) are allowed to look at the individual unblinded SUSAR cases.	Since the definition of every SUSAR requires knowledge of the precise investigational product **(or placebo)** used, unblinding will be carried out by named staff of the sponsor responsible for drug safety. Only ~~two members of the company staff (DSM or deputy)~~ **unblinded team members** are allowed to look at the individual unblinded SUSAR cases.	Wording regarding the process of unblinding for notification of a SUSAR was adjusted for more clarity and for correction of information given in the original Clinical Trial Protocol, version 1.0.
Minor change of wording.	Section 7.2.2 – Documentation and Reporting of Serious Adverse Events (new section 7.2.2.2 – Reporting Responsibili-ties of the Sponsor)	A specific SAE documentation form will be provided to the investigators.	A specific SAE ~~documentation~~ **reporting** form will be provided to the investigators.	Correction of imprecision in the original Clinical Trial Protocol, version 1.0.

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Change	**CSP sections affected**	**Original Text (CSP v1.0 / 25.03.2022)**	**Revised Text (CSP v2.0 / 21.12.2023)**	**Rationale**
Minor supplementation of wording.	Synopsis – Trial duration	Estimated start: 2nd quarter 2022 (first patient first visit [FPFV])	Estimated start **of trial**: 2nd quarter 2022 (first patient first visit [FPFV])	Wording has been added for clarification.
Minor supplementation of wording.	Section 5.2 – Characterisation of IMP	The characteristics of the trial medication (naronapride 10/20/40 mg tablets and corresponding placebo tablets) are displayed in the following tables:	The characteristics of the ~~trial medication~~**IMPs** (naronapride 10/20/40 mg tablets and corresponding placebo tablets) **and directions for intake of the IMP** are displayed in the following tables:	Wording has been added the sake of completeness.
Clarification on the receipt of a randomization list by the Drug Safety Department	Section 9.6 – Randomisation and Blinding	Three hardcopies of the randomisation list will be prepared and sealed by staff of CRO who is not involved in the trial conduct. One sealed list will be stored in the Sponsor's Dug Safety Department, one will be used by the Sponsor's quality control manager responsible for production and packaging of the IMPs, one will be used by the company performing packaging of the IMPs, where the randomisation list will not	~~Three~~ **Two** hardcopies of the randomisation list will be prepared and sealed by staff of CRO who is not involved in the trial conduct. One sealed list will ~~be stored in the Sponsor's Dug Safety Department, one will~~ be used by the Sponsor's quality control manager responsible for production and packaging of the IMPs, one will be used by the company performing packaging of the IMPs, where the randomisation list will not	Contrary to the statement in the original Clinical Trial Protocol, version 1.0, the Drug Safety Department did not receive a randomisation list. This was not planned at any time. To keep the responsible Drug Safety Manager blinded, the Drug Safety Department has received emergency envelopes that can be opened in individual cases to unblind a patient if necessary. Therefore, a

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		be accessible to others than production staff.	be accessible to others than production staff. **The responsible Drug Safety Manager at the Sponsor's Drug Safety Department will receive emergency envelopes to ensure the blinding.**	correct description was required.
Former sections 13.2 and 14.3 have been summarized to only one section (13.2). Specification / differentiation for Germany and other countries (subsections 14.3.1 and 14.3.2) was removed.	Section 13.2 – Independent Ethics Committees and National Competent Authorities and Section 14.3 – Regulatory Authorities Approval	13.2 Independent Ethics Committee In conformity with the national guidelines and the GCP provisions, the trial protocol, the patient information/informed consent form and any other document given to the patient will be submitted to an IEC before the start of the trial. Its advisory judgement will be heeded. [..] 14.3 Regulatory Authorities Approval [..] 14.3.2 Other Countries	13.2 Independent Ethics Committees **and National Competent Authorities** In conformity with the national guidelines and the GCP provisions, the trial protocol, the patient information/informed consent form and any other document given to the patient ~~will be~~ **has been** submitted to an IEC before the start of the trial. **The clinical trial in each of the participating countries will only start after having received an initial ethics approval.** ~~Its advisory judgement will be added.~~	The two sections were summarized to one for reasons of standardisation and to apply for both, Non-EU and EU countries. Consequently, specification for Germany was removed to keep the wording generally valid for all participating countries. Furthermore, wording of the section was specified to emphasize that the approval of the ethics committee is mandatory prior to the start of the trial.

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		The provisions for other countries will be followed, respectively.	**Furthermore, no patient may be included in the trial before the respective requirements of the national competent authorities are fulfilled.** ~~14.3 Regulatory Authorities Approval~~ ~~[..]~~ ~~14.3.2 Other Countries~~ ~~The provisions for other countries will be followed, respectively.~~	
Wording regarding data protection was supplemented by information about security measures for collection, processing, and storing study-related data electronically.	Section 17 – Patient Data and Data Protection	N/A	[..] **Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data.**	Information about information technology systems was added to specify security measures for electronical study-related data.
Clarification of wording regarding regulatory requirements for the	Title Page Protocol Signatures	This trial protocol has been reviewed and approved by the undersigned	This trial protocol has been reviewed and approved by the undersigned	Former wording was supplemented to be more

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Change	**CSP sections affected**	**Original Text (CSP v1.0 / 25.03.2022)**	**Revised Text (CSP v2.0 / 21.12.2023)**	**Rationale**
clinical trial.	Appendix A	persons/Coordinating Investigator. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.	persons/Coordinating Investigator. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements **concerning Clinical Trials of participating countries.**	precise about the named regulatory requirements.
Minor corrections / formatting errors	Synopsis Section 3.1.2 – Exclusion criteria	[..] 18. Any treatment within 2 weeks prior to BSL (visit 2) with medication that may alter gastrointestinal motility due to prokinetic/antiemetic effects: 19. Macrolide antibiotics (e.g., erythromycin), anti-malarials, anti-protozoals, anthelminthics, 20. Antidiarrheals and antispasmotics (e.g., butylscoplomaine), laxatives,	[..] 18. Any treatment within **three days prior to the screening GEBT and** 2 weeks prior to BSL (visit 2) with medication that may alter gastrointestinal motility due to prokinetic/ **inhibiting**/antiemetic effects: • Macrolide antibiotics (e.g., erythromycin), anti-malarials, anti-protozoals,	For harmonisation with listing of exclusion criteria in the Protocol synopsis (where ECs are numbered correctly). The correction of the numbering of ECs in section 6.3.1 is highlighted in turquoise in the TC version of the Clinical Trial Protocol, version 2.0.

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
		21. Opioids or cannabinoids, 22. Dopamine antagonists (e.g., metoclopramide, domperidone, alizapride), 23. 5-HT4 agonists (e.g., tegaserod, prucalopride), 24. 5-HT3 antagonists (e.g., tropisetron, ondansetron), 25. Anorectics (e.g., fenfluramine), 26. Other: aprepitant, lubiprostone, scopolamine (e.g., transdermal plaster). • H1-receptor antihistamines of first generation (e.g., doxylamine) within 2 weeks prior to BSL (visit 2) • Note: dimenhydrinate (cyclizine in the Netherlands, only) in the standard daily prescribed dose is allowed if not applied for more than 2 days per week in the two weeks prior to BSL (visit 2),	anthelminthics, • Antidiarrheals and antispasmotics (e.g., butylscoplomaine), laxatives, • Opioids or cannabinoids, • Dopamine antagonists (e.g., metoclopramide, domperidone, alizapride), • 5-HT4 agonists (e.g., tegaserod, prucalopride), • 5-HT3 antagonists (e.g., tropisetron, ondansetron), • Anorectics (e.g., fenfluramine), • **Systemic/oral anticholinergics (e.g., Solifenacin, Mebeverine); Exception: Inhaled parasympatholytics (e.g., ipratropiumbromide for COPD/Asthma) are allowed if used at standard stable doses,** • Other: aprepitant, lubiprostone,	

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
		• Dopamine agonists (e.g., cabergoline) within 2 weeks prior to BSL (visit 2), • Class I and class III antiarrhythmics (e.g., propafenone, amiodarone) within 4 weeks prior to BSL (visit 2), • (Atypic) neuroleptics (e.g., clozapine) within 4 weeks prior to BSL (visit 2), • Any treatment with GLP-1 analogues within 5 weeks prior to BSL (visit 2), • Use of any over-the-counter medication within two weeks prior to BSL (visit 2) that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin [Carmenthin®], STW5 [Iberogast®]),	scopolamine (e.g., transdermal plaster). 19. H1-receptor antihistamines of first generation (e.g., doxylamine) within 2 weeks prior to BSL (visit 2) ~~Note~~**Exception**: **Locally sourced OTC preparations against nausea (preferably** dimenhydrinate ~~(~~**alternatively** cyclizine **or meclozine** ~~in the Netherlands, only)~~ **as rescue medication** in the standard daily prescribed dose ~~is~~**are** allowed if not applied for more than 2 days per week ~~in the two weeks prior to BSL (visit 2)~~**from SCR 2 (V1) onwards**, 20. Dopamine agonists (e.g., cabergoline) within 2 weeks prior to BSL (visit 2), 21. Class I and class III antiarrhythmics (e.g., propafenone, amiodarone) within 4 weeks prior to BSL (visit 2),	

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Change	CSP sections affected	Original Text (CSP v1.0 / 25.03.2022)	Revised Text (CSP v2.0 / 21.12.2023)	Rationale
		• Begin of treatment or treatment more than once per week in the last 3 months prior to BSL (visit 2) with 5-HT1-receptor agonists (including but not limited to sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan), 27. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: serotonin reuptake inhibitors, H2R antagonists, PPIs, calcium channel blockers, tricyclic antidepressants (in excess of 75 mg daily) and tetracyclic antidepressants, Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: systemic corticosteroids or nonsteroidal anti-inflammatory drugs	22. (Atypic) neuroleptics (e.g., clozapine) within 4 weeks prior to BSL (visit 2), 23. Any treatment with GLP-1 analogues within 5 weeks prior to BSL (visit 2), 24. Use of any over-the-counter medication within two weeks prior to BSL (visit 2) that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin [Carmenthin®], STW5 [Iberogast®]), 25. Begin of treatment or treatment more than once per week in the last 3 months prior to BSL (visit 2) with 5-HT1-receptor agonists (including but not limited to sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan), 26. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the	

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		(NSAIDs) with the exception of additional occasional use of NSAIDs for e.g., mild headache or musculoskeletal pain, 28. [..]	following drugs: serotonin reuptake inhibitors, H_2R antagonists, PPIs, calcium channel blockers, tricyclic antidepressants (in excess of 75 mg daily) and tetracyclic antidepressants, 27. Begin of treatment or altered doses within 2 weeks prior to BSL (visit 2) of one of the following drugs: systemic corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) with the exception of additional occasional use of NSAIDs for e.g., mild headache or musculoskeletal pain, 28. [..]	
Correction of a formatting error for the subsections in section 8.2	Section 8.1.1 – Termination of the Whole Trial 8.1.2 – Termination of the Trial at an	8.1.1 Termination of the Whole Trial 8.1.2 Termination of the Trial at an Investigational Site	8.~~1~~**2**.1 Termination of the Whole Trial 8.~~1~~**2**.2 Termination of the Trial at an Investigational Site	Eliminate formatting errors

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	Investigational Site			
Numbering of footnotes adapted	Flow Chart	N/A	Changes can be traced back via track change mode.	With introducing a new footnote for the Flow Chart, the sequence and numbering of footnotes changed as a consequence.
Replacement of the tern 'Study participant' by 'Trial participant '	Flow Chart (Footnote 9 [former 10]) Synopsis - Exclusion Criteria Section 3.1 – Patient selection Section 3.1.2 – Exclusion citeria Section 6.4.6.1 – Safety assessments	N/A	Changes can be traced back via track change mode.	The term ‘Study participant’ was replaced by ‘Trial participant’ in the named sections for harmonization of wording (Trial participant) throughout the protocol. These changes are not displayed in this summary but can be traced back via the tracked change version of the Clinical Trial Protocol.

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N/A	All sections	N/A	Changes can be traced back via track change mode.	Some minor corrections like the addition of missing abbreviations, upper case and lower case letters, and the correction of typos have been implemented in addition. These changes are not displayed in this summary but can be traced back via the tracked change version of the Clinical Trial Protocol.

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List of Changes with Clinical Trial Protocol for the USA – Final Version 1.0 / 07.03.2024 (also applicable for the Clinical Trial Protocol for Australia (AUS) – Final Version 1.0 / 18.03.2014)

The following overview outlines the changes implemented with the local version of the Clinical Trial Protocol for the USA (version 1.0 / 07.03.2024) based on the integrated Clinical Trial Protocol (version 2.0 / 21.12.2023) for the NAT-19/GPX trial, which became necessary to take account of objections raised by the U.S. Department of Health and Human Services Food and Drug Administration (FDA) during IND submission (IND 169456).

The individual changes that have been made to the protocol to address the FDA's objections are detailed in the table below; the additions are being highlighted in ***bold italics***.

Change	**CTP sections affected**	**Original Text (CTP v2.0 / 21.12.2023)**	**Revised Text (CTP for the USA v1.0 / 07.03.2024 and CTP for Australia v.1.0 / 18.03.2024)**	**Rationale**
Inclusion of AESI with instructions for monitoring and managing.	Section 7.1.2 – Serious Adverse Events	Section 7.1.2 Serious Adverse Events […] Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent	Section 7.1.2 Serious Adverse Events ***(SAE) and Adverse Events of Special Interest (AESI)*** […] Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may	As per FDA request received on 04 March 2024 risks associated with 5-HT4 agonists have been added as AESI: • QT prolongation • Serotonin syndrome • Drug-Induced Liver Injury (DILI) • Major Adverse Cardiovascular Events (MACE)

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		one of the other outcomes listed in the definition above. These should also usually be considered serious. If unintended pregnancy occurs between the first administration of the IMP (V2) and up to 28 days of last dose of IMP, pregnancy has to be reported in the same timely way as an SAE. Spontaneous miscarriages should also be reported and handled as SAEs (see section 7.1.4 for details on handling of pregnancies). […]	require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. ***An adverse event of special interest (AESI) is an adverse event which can be serious or non-serious and which is of scientific and medical concern specific to the product for which ongoing monitoring and rapid communication is considered appropriate. Such events may require further investigation in order to characterize and understand them.*** ***The following adverse events are considered as being of special interest:*** • ***QT prolongation:*** ***A QTcF prolongation of > 450 msec for males and > 470 msec for females is considered as an AESI. In case of QTcF prolon-***	• Volume depletion associated with diarrhea • Suicidal ideation and behavior

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Change	CTP sections affected	Original Text (CTP v2.0 / 21.12.2023)	Revised Text (CTP for the USA v1.0 / 07.03.2024 and CTP for Australia v.1.0 / 18.03.2024)	Rationale
			gation of > 500 msec or QTcF increase of 60 ms compared to baseline level, IMP has to be discontinued (see also section 8.1). • ***Serotonin syndrome:*** ***A serotonin syndrome defined according to Hunter Serotonin Toxicity Criteria (Dunkley et al, 2003) is considered as an AESI, if the following applies:*** 1. ***IF (spontaneous clonus = yes) THEN serotonin toxicity =YES*** 2. ***ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES*** 3. ***ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES***	

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Change	CTP sections affected	Original Text (CTP v2.0 / 21.12.2023)	Revised Text (CTP for the USA v1.0 / 07.03.2024 and CTP for Australia v.1.0 / 18.03.2024)	Rationale
			4. *ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES* 5. *ELSE IF (hypertonic = yes) AND (temperature > 38^{0}C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] then serotonin toxicity = YES* 6. *ELSE serotonin toxicity = NO* ***In case of serotonin syndrome, IMP has to be discontinued (see also section 8.1).*** • ***Drug-Induced Liver Injury (DILI):*** ***DILI is defined as a liver damage or dysfunction caused by the use of a medication, OTC, dietary supplement or herbal. In some cases, DILI is associated with hepatotoxicity. Aminotransferase (ALT or AST)***	

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Change	CTP sections affected	Original Text (CTP v2.0 / 21.12.2023)	Revised Text (CTP for the USA v1.0 / 07.03.2024 and CTP for Australia v.1.0 / 18.03.2024)	Rationale
			levels greater than the 3 x ULN are considered as an AESI. In this case the following measures are to be taken and further data have to be obtained respectively to detect a potential DILI: – ***Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.*** – ***Obtaining a more detailed history of symptoms and prior or concurrent diseases.*** – ***Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement***	

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			preparations), alcohol use, recreational drug use, and special diets. – ***Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.*** – ***Obtaining a history of exposure to environmental chemical agents.*** – ***Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).*** – ***Considering gastroenterology or hepatology consultations.*** • ***In case of Drug-Induced Liver Injury according to FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical***	

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			Evaluation, July 2009, IMP has to be discontinued (see also section 8.1). • ***Major Adverse Cardiovascular Events (MACE):*** ***4-point MACE (myocardial infarction, stroke, transient ischemic attack (TIA), or angina pectoris) is considered as an AESI. In case a confirmed myocardial infarction or stroke is experienced, IMP has to be discontinued. If a patient is diagnosed with TIA or angina pectoris, further diagnostic measures to evaluate the cause of the event should be performed. Further treatment with IMP is upon decision of the investigator.*** • ***Volume depletion associated with severe diarrhea:*** ***Volume depletion associated with severe diarrhea (i.e. patient***	

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			has signs of dehydration in the form of hypotension or even syncopal events preventing the patient from normal daily activities) is considered an AESI. Investigator should check for signs at all visits during the treatment phase. Patients with an AESI of severe diarrhea associated with volume depletion at any time during the treatment phase will be discontinued from the IMP. • ***Suicidal Ideation and Behaviour:*** ***Clinical worsening of depression and emergence of suicidal thoughts and behavior is considered as an AESI. Patients and patients with a history of depression/mood disorder should be monitored carefully for clinical signs of a worsening of depression and the emergence of suicidal thoughts and behaviors***	

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			at each visit. The patient's diary ePROs (EQ-5D-5L, PAGI-QoL) might give direct or indirect hints to such a worsening. In that case, patients should immediately discontinue IMP and contact their healthcare provider to receive appropriate treatment. ***All AESI have to be reported in the same timely manner as an SAE (see section 7.2.2.1).*** If unintended pregnancy occurs between the first administration of the IMP (V2) and up to 28 days of last dose of IMP, pregnancy has to be reported in the same timely way as an SAE. Spontaneous miscarriages should also be reported and handled as SAEs (see section 7.1.4 for details on handling of pregnancies). […]	

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	Section 7.2.2.1 – Investigator's Reporting Responsibilities for SAEs	Upon enrolment in the trial, the patients will be instructed to contact the investigator if a serious or unexpected AE occurs during the screening phase, the treatment phase, and during 4 weeks after EOT/WD visit, so that appropriate measures can be taken. **Any SAE (including death, irrespective of the cause) occurring during the screening phase, the double-blind treatment phase, or follow-up phase must be reported by the investigator to the project manager of the CRO and in parallel to the Sponsor's Drug Safety immediately (without undue delay but not later than 24 hours) after it comes to light, irrespective of its relationship with the administration of the IMP (minimum information required: investigator's**	Upon enrolment in the trial, the patients will be instructed to contact the investigator if a serious***, ~~or~~*** unexpected ***or*** AE ***of special interest*** occurs during the screening phase, the treatment phase, and during 4 weeks after EOT/WD visit, so that appropriate measures can be taken. **Any SAE (including death, irrespective of the cause) *or AESI (whether serious or non-serious)* occurring during the screening phase, the double-blind treatment phase, or follow-up phase must be reported by the investigator to the project manager of the CRO and in parallel to the Sponsor's Drug Safety immediately (without undue delay but not later than 24 hours) after it comes to light, irrespective of its relationship with the administration of the**	

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		name/trial site, screening number, visit kit number, date of first dose, date of last dose, date of event, description of event, causality assessment, and countermeasures). **[…]** A specific SAE reporting form will be provided to the investigators. In case of an SAE, this form should be completed, checked, and signed by the investigator as an initial report, and **sent** (via fax or scanned e-mail) **immediately (without undue delay) after coming to light to the trial coordinating CRO and** the sponsor's Drug Safety in parallel. If required, a follow-up report including all new information obtained on the SAE must be reported using an updated version of the "SAE form" and must be sent again to both parties. SAE information in	**IMP (minimum information required: investigator's name/trial site, screening number, visit kit number, date of first dose, date of last dose, date of event, description of event, causality assessment, and countermeasures).** **[…]** A specific SAE reporting form will be provided to the investigators. In case of an SAE ***or an AESI***, this form should be completed, checked, and signed by the investigator as an initial report, and ***sent*** (via fax or scanned e-mail) **immediately (without undue delay) after coming to light to the trial coordinating CRO and** the sponsor's Drug Safety in parallel. If required, a follow-up report including all new information obtained on the SAE must be reported using an updated version	

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		eCRF should be updated accordingly, when applicable. […]	of the "SAE form" and must be sent again to both parties. SAE information in eCRF should be updated accordingly, when applicable.	
	Section 8 – Withdrawal Criteria Section 8.1 – Criteria in Individual Cases	8 Withdrawal Criteria 8.1 Criteria in Individual Cases Any patient can withdraw from the trial at any time without personal disadvantages and without having to give a reason. The investigator can also discontinue the trial after considering the benefit/risk ratio if he/she no longer considers the further participation of the patient justifiable. For patients withdrawn prior to randomisation, a brief reason should be given why the patient is a screening failure (e.g., violation of in-/exclusion criteria (to be specified), patient's request to withdraw). For all randomised patients who are prematurely	8 ***Criteria for Premature Treatment Discontinuation and*** Withdrawal ~~***Criteria***~~ 8.1 Criteria in Individual Cases Any patient can ***prematurely discontinue the treatment with the IMP or*** withdraw from the trial at any time without personal disadvantages and without having to give a reason. The investigator can also discontinue the ~~***trial***~~ ***treatment*** after considering the benefit/risk ratio if he/she no longer considers the further ~~***participation of the patient***~~ ***treatment*** justifiable. For patients withdrawn prior to randomisation, a brief reason should be given why the patient is a screening failure (e.g., violation	

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		withdrawn, the date of withdrawal and the primary reason for the withdrawal, as well as the observations available at the time of withdrawal are to be documented in the eCRF. Reasons leading to the withdrawal of a randomised patient can include the following (**only <u>one</u> primary reason must be determined**): • **Lack of clinical efficacy**, e.g.: – Progress of trial disease defined as not bearable clinical symptoms compared to baseline (over 2 subsequent weeks) • **Intolerable AE** (to be specified), which precludes, in the opinion of the investigator, the further trial participation of a patient, In case of a clinically significant QTcF -prolonga-tion during the course of the trial, the investigator in	of in-/exclusion criteria (to be specified), patient's request to withdraw). For all randomised patients who are ***prematurely discontinued from the treatment with the IMP or who are*** prematurely withdrawn from the trial, the date of ***premature discontinuation from treatment or*** withdrawal and the primary reason for the ***premature discontinuation of treatment or*** withdrawal, as well as the observations available at the time of ***premature discontinuation of treatment or*** withdrawal are to be documented in the eCRF. Reasons leading to the ***premature discontinuation of treatment or*** withdrawal from trial of a randomised patient can include the following (**only <u>one</u> primary reason must be determined**): • **Lack of clinical efficacy**, e.g.: – Progress of trial disease defined as not bearable	

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		consultation with the DSM of the sponsor and the responsible MM has to decide whether the patient should continue with the IMP treatment or not. • **Lack of patient's cooperation**, e.g.: – Patient's request to withdraw, – […]	clinical symptoms compared to baseline (over 2 subsequent weeks) • **Intolerable AE** (to be specified), which precludes, in the opinion of the investigator, ~~***the***~~ further ~~***trial participation***~~ ***treatment with the IMP or further trial participation*** of a patient, • In case of a clinically significant QTcF-prolongation during the course of the trial, the investigator in consultation with the DSM of the sponsor and the responsible MM has to decide whether the patient should continue with the IMP treatment or not. ***In case of QTcF prolongation of > 500 msec or QTcF increase of 60 ms compared to baseline level, IMP has to be discontinued.***	

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			• ***In case of occurrence of Serotonin Syndrome defined according to Hunter Serotonin Toxicity Criteria, IMP has to be discontinued (see also section 7.1.2).*** • ***In case of suspected Drug-Induced Liver Injury (DILI) as defined below*** – ***ALT or AST > 8 x ULN or*** – ***ALT or AST > 5 x ULN for more than 2 weeks or*** – ***ALT or AST > 3 x ULN and (TBL > 2 x ULN or INR > 1.5) or*** – ***ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) treatment with the IMP has to be discontinued.*** • ***In case of a confirmed myocardial infarct or stroke,***	

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			IMP has to be discontinued (see also section 7.1.2). • ***In case of severe diarrhea associated with volume depletion, IMP has to be discontinued (see also section 7.1.2).*** • ***In case of clinical worsening of depression and emergence of suicidal thoughts and behavior, IMP has to be discontinued (see also section 7.1.2).*** • **Lack of patient's cooperation**, e.g.: – Patient's request to withdraw, – […]	
Prolactin levels above the normal value at the end of treatment have been defined as AESI and appropriate measures have been introduced to further evaluate these events.	Section 7.1.2 – Serious Adverse Events	Section 7.1.2 Serious Adverse Events […] Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations,	Section 7.1.2 Serious Adverse Events ***(SAE) and Adverse Events of Special Interest (AESI)*** […] Medical and scientific judgement should be exercised in deciding	Based on histopathological changes (lobular / mucinous hyperplasia, vacuolation) observed in pre-clinical studies the FDA in the request for information received on

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		such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. […]	whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. […] • ***Prolactin value above normal range at EOT*** ***To further investigate increased prolactin levels, values above normal range at EOT are considered as AESI.*** ***In such cases, the investigator should further evaluate the cause of the event as follows:***	March 6, 2024, asked to specifically include a targeted physical examination for mammary gland changes. From our point of view a targeted physical examination is not sensitive enough to detect the above-mentioned hyperplastic changes (observed on histopathological and not on clinical level) reliably and was therefore not added to the protocol. Due to the fact, that the described histopathological changes are compatible with effects of increased prolactin (hyperprolactinemia) the protocol already foresees the measurement of prolactin to detect

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			– ***by questioning the patient for potentially known reasons and/or*** – ***by checking concomitant medication and underlying diseases and/or*** – ***by referral to a medical specialist (e.g., gynecologist or endocrinologist) for further clarification.*** ***If no root cause can be identified, the event should be followed-up by a prolactin re-test to assess the outcome of the event.*** ***This re-test should be performed as part of an unscheduled visit 2 weeks after EOT. As prolactin shows a circadian rhythm with highest concentrations in the morning, sampling should preferably be performed in the morning under fasting conditions (or at the same time as for the previous test).***	potential increases of prolactin levels following the treatment with the IMP. To not only evaluate potential prolactin changes (EOT vs pre-treatment) on laboratory level it has been decided to consider any value of prolactin above normal range at EOT visit as an AESI in addition.

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			[…]	
Minor editorial changes	All sections	N/A	Changes can be traced back via track change mode.	Minor editorial amendments such as addition of missing abbreviations and insertion of additional cross-references.

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List of Changes with Clinical Trial Protocol for the USA – Final Version 2.0 / 30.07.2024

The following overview outlines the changes implemented with the Clinical Trial Protocol for the USA (version 2.0 / 30.07.2024) based on the FDA's Study May Proceed correspondence dated March 26, 2024, for Dr. Falk Pharma GmbH's (Dr. Falk's) IND 169456 to initiate the Phase IIb clinical trial NAT-19/GPX.

The individual changes that have been made to the Clinical Trial Protocol to address the FDA's recommendations are detailed in the table below; the additions are being highlighted in ***bold italics***. The same applies to additional changes that have been implemented for logistical and safety reasons or to clarify the original intent of the protocol.

Change	**CTP sections affected**	**Original Text (CTP for the USA v1.0 / 07.03.2024)**	**Revised Text (CTP for the USA v2.0 / 30.07.2024)**	**Rationale**
EC #15, #18 and #28 have been changed in accordance with the with the objections raised by the FDA.	Synopsis - Exclusion Criteria and Section 3.1.2 - Exclusion Criteria	15. ALT or ALP >2.5 x upper limit of normal (ULN) at SCR 2 (visit 1),	15. ALT or ALP >2.5 x upper limit of normal (ULN) at SCR 2 (visit 1)***, or any degree of hepatic impairment based on Child-Pugh scores (Child-Pugh A, B and C)***,	As part of the "Study May Proceed Letter", the FDA recommended in its first comment that various exclusion criteria should be modified for safety reasons. The sponsor is following these suggestions with this amendment to the Clinical Trial Protocol.

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	Synopsis - Exclusion Criteria and Section 3.1.2 - Exclusion Criteria	18. Any treatment within three days prior to the screening GEBT and 2 weeks prior to BSL (visit 2) with medication that may alter gastrointestinal motility due to prokinetic/inhibiting/antieme-tic effects:[…],	18. Any treatment within three days ***or 5 half-lives whichever is longer*** prior to the screening GEBT and 2 weeks prior to BSL (visit 2) with medication that may alter gastrointestinal motility due to prokinetic/inhibiting/antieme-tic effects: […],	
		28. Any medication with known potential of clinically relevant P-gp inhibition that might lead to increased or prolonged effects of the Investigational Medicinal Product (IMP) under careful risk-benefit analysis at the discretion of the investigator,	28. Any medication with known potential of clinically relevant P-gp inhibition that might lead to increased or prolonged effects of the Investigational Medicinal Product (IMP) ***within 2 weeks or 5-half-lives whichever is longer prior to BSL (visit 2)*** under careful risk-benefit analysis at the discretion of the investigator,	

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Introducing the interim analysis as an optional measure	Synopsis - Trial design	[…] The trial will be performed according to a multi-arm, 2-stage, group-sequential adaptive design with the option of sample size adjustment, treatment arm selection, or early termination after the planned interim analysis (IA). […]	[…] ***An interim analysis (IA) has been planned as an option for this trial, but only if warranted by the actual recruitment status. Recruitment will be monitored in a blinded fashion and the decision on performing the interim analysis will solely be made on blinded information. In case the IA will be performed, the~~The~~*** trial will be performed according to a multi-arm, 2-stage, group-sequential adaptive design with the option of sample size adjustment, treatment arm selection, or early termination after the planned ***~~interim analysis (IA)~~***. […]	Based on the objections raised by the FDA in comment 8, the sponsor has decided to conduct the originally planned interim analysis only if this analysis seems to be reasonable at the time of randomization of the last patient planned for the interim analysis based on the actual recruitment progress at that time and the expected end of recruitment.
	Synopsis - Statistical analysis	[…] The planned IA that primarily aims to verify the assumptions of the sample size calculation is planned to be conducted after 60% of participants (= 192 FAS-evaluable participants) have	[…] The planned IA that primarily aims to verify the assumptions of the sample size calculation is planned to be conducted after 60% of participants (= 192 FAS-evaluable participants) have	

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	Synopsis - Statistical analysis	completed their treatment. A sponsor-independent Data Monitoring Committee (IDMC) will review unblinded data at the IA and will make recommendations to the sponsor regarding: […]	completed their treatment***, but only if warranted by the actual recruitment status***. A sponsor-independent Data Monitoring Committee (IDMC) will review unblinded data at the IA and will make recommendations to the sponsor regarding: […]	
	Section 3.3 - Sample Size	The trial will be performed according to a two-stage, multi-arm, group-sequential adaptive design with possible sample size adjustment after the planned interim analysis (IA). The IA will be carried out when the data of 192 full analysis set (FAS)-evaluable patients of the double-blind phase are available (i.e., after completion of the EOT/WD visit; V6). If the trial is continued until completion and no adaptation is made at the interim analysis, the sample size will be 320 (4 x 80) FAS-evaluable patients. […]	The trial ***~~will be performed~~has been planned*** according to a two-stage, multi-arm, group-sequential adaptive design with possible sample size adjustment ***~~after the planned~~following an*** interim analysis (IA). ***Only if warranted by recruitment status, an~~The~~*** IA will be carried out when the data of 192 full analysis set (FAS)-evaluable patients of the double-blind phase are available (i.e., after completion of the EOT/WD visit; V6). ***Without sample size adjustment as part of an optional~~If the trial is continued until completion and no adaptation is made at the~~***	

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	Section 3.3 - Sample Size		interim analysis, the sample size will be 320 (4 x 80) FAS-evaluable patients. […]	
	Section 4 - Trial Design	[…] The trial will be performed according to a multi-arm, 2-stage, group-sequential adaptive design with the option of sample size adjustment, treatment selection, or early termination after the planned IA. Participants stratified by type of gastroparesis will be assigned to one of the four treatment groups via a central randomisation procedure using a 1:1:1:1 balance. To guarantee the double-blinding, the trial will be conducted using placebo tablets identical in appearance, shape, size, and taste to active substance. Therefore, neither the investigator nor the patient will have knowledge of the patients' respective assignment to any of the treatment groups (A, B, C or	[…] The trial ~~***will be performed***~~***has been planned*** according to a multi-arm, 2-stage, group-sequential adaptive design with the option of sample size adjustment, treatment selection, or early termination ~~***after the planned IA***~~***in case that an IA is deemed feasible, as further detailed in section 9.3.3***. Participants stratified by type of gastroparesis will be assigned to one of the four treatment groups via a central randomisation procedure using a 1:1:1:1 balance***, which could possibly shift in favour of the placebo, if one or more of the active treatment groups should be closed as a result of the optionally planned interim analysis***. To guarantee the	

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	Section 4 - Trial Design	D): […]	double-blinding, the trial will be conducted using placebo tablets identical in appearance, shape, size, and taste to active substance. Therefore, neither the investigator nor the patient will have knowledge of the patients' respective assignment to any of the treatment groups (A, B, C or D): […]	
	Section 7.5 - DSMB and IDMC	[…] The members of the DSMB will also constitute the Independent Data Monitoring Committee (IDMC) responsible to conduct and review the efficacy and safety results at the planned IA (see section 9.3.3). The IDMC will have access to unblinded data. […] Like the DSMB the IDMC will act according to a written charter and will prepare written minutes	[…] The members of the DSMB will also constitute the Independent Data Monitoring Committee (IDMC) responsible to conduct and review the efficacy and safety results at the ***optionally*** planned IA (see section 9.3.3). ***In case an IA is performed, only the members of the~~The~~*** IDMC will have access to unblinded data. […] Like the DSMB and the IDMC ***(in case that an interim analysis will be conducted)*** will act according to a written charter and	

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	Section 7.5 - DSMB and IDMC	of its meetings. […] […] Before unblinding, a Statistical Analysis Plan (SAP) will be prepared for the interim analysis and approved by the Sponsor. […] At the planned IA, the randomisation code of the patients to be included in the IA will be unblinded to the IDMC members. The unblinded biostatistician will electronically match the random code of the patients to be included in the IA with the trial data and will send confidentially the results and a brief statistical report summarising the results of the IA to the other IDMC members.	will prepare written minutes of its meetings. […] […] Before unblinding ***and in case an IA is performed*** **an interim** Statistical Analysis Plan (***i***SAP)***, specifying the details regarding the statistical analysis*** will be prepared ~~for the interim analysis~~ and approved by the Sponsor. […] At the ***optionally*** planned IA, the randomisation code of the patients to be included in the IA will be unblinded to the IDMC members. The unblinded biostatistician will electronically match the random code of the patients to be included in the IA with the trial data and will send confidentially the results and a brief statistical report summarising the results of the IA to the other IDMC members. ***The results of the IA will be kept under locked conditions until final unblinding at the end of the***	

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	Section 7.5 - DSMB and IDMC		***trial and then forwarded to the sponsor for TMF filing.***	
	Section 8.2.1 - Termination of the Whole Trial	[…] Details on the possibility to stop the trial based on results of the interim analysis are described in section 9.3.3.	[…] Details on the possibility to stop the trial based on results of the interim analysis ***(planned to be conducted optionally)*** are described in section 9.3.3.	
	Section 9.3.1.1 - General Approach	The primary efficacy endpoint will be subjected to a confirmatory statistical analysis ($\alpha = 0.025$, one-sided) for the three test groups in the context of a multi-arm, two-stage, group-sequential adaptive trial design[33] for testing in many-to-one comparisons as described in section 9.3.3. One interim analysis is planned. For the final analysis, all patients qualifying for the different analysis sets will be included in the analysis. The evaluation of the primary efficacy endpoint at interim analysis will	The primary efficacy endpoint will be subjected to a confirmatory statistical analysis ($\alpha = 0.025$, one-sided) for the three test groups in the context of a multi-arm, two-stage, group-sequential adaptive trial design[33] for testing in many-to-one comparisons as described in section 9.3.3. One ***optional*** interim analysis is planned***, which will only be conducted, if warranted by actual recruitment status***. For the final analysis, all patients qualifying for the different analysis sets will be included in the analysis. The	

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	Section 9.3.1.1 - General Approach	be performed according to the primary estimand. […] To date, it is not clear which of the three dose strengths (10, 20 or 40 mg TID) will be more efficacious and therefore no a-priori ordering of hypotheses is possible. The null hypotheses will be tested using the Dunnett procedure, which preserves the familywise α-level in this many-to-one comparison. Efficacy for at least one treatment arm will be proven after the interim analysis if the respective test statistic resulting from the inverse normal method exceeds the critical value determined by the O'Brien-Fleming α-spending function.	evaluation of the primary efficacy endpoint at interim analysis ***(if applicable)*** will be performed according to the primary estimand. […] To date, it is not clear which of the three dose strengths (10, 20 or 40 mg TID) will be more efficacious and therefore no a-priori ordering of hypotheses is possible. The null hypotheses will be tested using the Dunnett procedure, which preserves the familywise α-level in this many-to-one comparison. ***If an interim analysis is performed, the*** efficacy~~Efficacy~~ for at least one treatment arm will be proven after the interim analysis if the respective test statistic resulting from the inverse normal method exceeds the critical value determined by the O'Brien-Fleming α-spending function.	

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	Section 9.3.2 - Evaluation of the Secondary Endpoints and Exploratory Endpoints	[…] All p-values resulting from statistical tests will be interpreted in an exploratory sense. Supportive and sensitivity analyses will be performed after the final analysis or, if the trial was stopped prematurely, after the interim analysis.	[…] All p-values resulting from statistical tests will be interpreted in an exploratory sense. Supportive and sensitivity analyses will be performed after the final analysis or, if the trial was stopped prematurely, after the interim analysis ***(if applicable)***.	
	Section 9.3.3 - Interim Analysis	N/A	***Optionally the trial will include an interim analysis (IA).*** ***The IA is planned to be carried out when the first 192 consecutively randomized FAS-patients have reached their primary endpoint at EOT/WD (V6) (60% of the overall planned number of patients, information rate: 0.60), but only if warranted by the actual recruitment status. Recruitment will be monitored in a blinded fashion and the decision on performing the IA will solely be made on blinded information at the time of randomization of the last patient***	

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	Section 9.3.3 - Interim Analysis		***scheduled for the interim analysis.*** ***The decision on whether or not to conduct an IA will be made by the sponsor upon randomization of the last patient scheduled for IA.*** ***Based on the calculated timelines for the conduct of the IA and based on the recruitment progress within the last 3 months, an IA will only be conducted if the results from the IA can be obtained at least 4 weeks prior to the projected inclusion of the last patient (LPI = 320).*** ***In case an optional interim analysis will be performed, the*** ~~***The***~~ trial will be conducted according to a 2-stage group sequential adaptive test design with O'Brien and Fleming shaped boundaries with possible sample size adaptation and treatment arm selection after the interim analysis.	
		The trial will be conducted according to a 2-stage group sequential adaptive test design with O'Brien and Fleming shaped boundaries with possible sample size adaptation and treatment arm selection after the interim analysis.		

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	Section 9.3.3 - Interim Analysis	[…] The interim analysis is justified according to the 'Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design' (CHMP/EWP/2459/02)[34] because current knowledge on the effect size of the treatment groups is limited. […] The interim analysis is planned to be performed after 192 FAS-evaluable participants have reached the EOT/WD (V6) (60% of the overall planned number of patients, information rate: 0.60). Recruitment of patients will be continued during the performance of the interim analysis. […] The interim analysis will be performed by an unblinded biostatistician, and the results and a short statistical report will be	[…] ***Planning a possible the~~The~~*** interim analysis is justified according to the 'Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design' (CHMP/EWP/2459/02)[34] because current knowledge on the effect size of the treatment groups is limited. […] ***~~The interim analysis is planned to be performed after 192 FAS-evaluable participants have reached the EOT/WD (V6) (60% of the overall planned number of patients, information rate: 0.60).~~*** Recruitment of patients will be continued during the performance of the interim analysis. […] ***If being conducted, the~~The~~*** interim analysis will be performed by an unblinded biostatistician, and the results and	

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	Section 9.3.3 - Interim Analysis	provided to an IDMC. The recommendations of the IDMC may include stopping the whole trial or treatment arms for early efficacy if the inverse normal test statistic(s) exceed(s) the critical value determined by the O'Brien-Fleming α-spending function and actual information fraction.	a short statistical report will be provided to an IDMC. The recommendations of the IDMC may include stopping the whole trial or treatment arms for early efficacy if the inverse normal test statistic(s) exceed(s) the critical value determined by the O'Brien-Fleming α-spending function and actual information fraction.	
	Section 9.4 - Sample Size Calculation	[…] The trial will be performed according to a 2-stage multi-arm group-sequential adaptive design with the option of sample size adjustment, stopping of treatment arms, or early stopping of the trial for efficacy, futility, or safety after the planned interim analysis. There are no binding stopping rules for futility boundaries. The interim analysis is planned to be performed after 60% of the planned number of randomised patients have completed the trial (information rates: 0.6, 1.0). […]	[…] The trial ***~~will be performed~~has been planned*** according to a 2-stage multi-arm group-sequential adaptive design with the option of sample size adjustment, stopping of treatment arms, or early stopping of the trial for efficacy, futility, or safety after the planned interim analysis. There are no binding stopping rules for futility boundaries. ***If warranted by the actual recruitment status, the~~The~~*** interim analysis is planned to be performed after 60% of the planned number of randomised	

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	Section 9.4 - Sample Size Calculation		patients have completed the trial (information rates: 0.6, 1.0). […]	
Reference to the IDMC Charter and the interim SAP (iSAP) added.	Section 7.5 - DSMB and IDMC	[…] The members of the DSMB will also constitute the Independent Data Monitoring Committee (IDMC) responsible to conduct and review the efficacy and safety results at the planned IA (see section 9.3.3). The IDMC will have access to unblinded data. Based on the results of the interim analysis the IDMC will submit its recommendations in written form to the Sponsor who is responsible to respond to the recommendations of the IDMC and to take appropriate action. Like the DSMB the IDMC will act according to a written charter and will prepare written minutes	[…] The members of the DSMB will also constitute the Independent Data Monitoring Committee (IDMC) responsible to conduct and review the efficacy and safety results at the ***optionally*** planned IA (see section 9.3.3). ***In case an IA is performed, only the members of the~~The~~*** IDMC will have access to unblinded data. Based on the results of the interim analysis ***and the underlying decision tree as specified in the IDMC charter*** the IDMC will submit its recommendations in written form to the Sponsor who is responsible to respond to the recommendations of the IDMC and to take appropriate action. Like the DSMB the IDMC ***(in case that an interim analysis will be conducted)*** will act according	To account for the objections raised by the FDA with comment 8, further details regarding the planned interim analysis have been added, including references to related documents, i.e. the IDMC Charter and the interim SAP (iSAP).

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	Section 7.5 - DSMB and IDMC	of its meetings. The charter of the IDMC determines the members of the IDMC, their responsibility, and data flow. The charter will be stored in the TMF. Specifically, the IDMC will maintain records of its meetings that become part of the TMF when the trial is complete. […] Before unblinding, a Statistical Analysis Plan (SAP) will be prepared for the interim analysis and approved by the Sponsor. At the planned IA, the randomisation code of the patients to be included in the IA will be unblinded to the IDMC members. The unblinded biostatistician will electronically match the random code of the patients to be included in the IA with the trial data and will send confidentially the results and a brief statistical report	to a written charter and will prepare written minutes of its meetings. The charter of the IDMC determines the members of the IDMC, their responsibility, and data flow. The charter will be stored in the TMF. Specifically, the IDMC will maintain records of its meetings that become part of the TMF when the trial is complete. […] Before unblinding ***and in case an IA is performed*** **a*n interim*** Statistical Analysis Plan (***i***SAP)***, specifying the details regarding the statistical analysis*** will be prepared and approved by the Sponsor. ***An SAP for the final analysis will be prepared and approved by the Sponsor before unblinding.*** At the ***optionally*** planned IA, the randomisation code of the patients to be included in the IA will be unblinded to the IDMC members. The unblinded	

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	Section 7.5 - DSMB and IDMC	summarising the results of the IA to the other IDMC members.	biostatistician will electronically match the random code of the patients to be included in the IA with the trial data and will send confidentially the results and a brief statistical report summarising the results of the IA to the other IDMC members. ***The results of the IA will be kept under locked conditions until final unblinding at the end of the trial and then forwarded to the sponsor for TMF filing.***	

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	Synopsis – Statistical analysis Section 9.3.3 - Interim Analysis	The interim analysis aims at: 1. Verifying the assumptions of the sample size calculation or recalculating sample size based on the effect size estimations of the interim analysis 2. Investigating which treatment arm, if applicable, should be stopped after the interim analysis 3. […] […] Rejection of a null hypothesis will be possible at the interim analysis if the p-values with respect to the null hypothesis and all logically related hypotheses fall below α_1, where α_1 is determined by the O'Brien-	The interim analysis aims at: 1. Verifying the assumptions of the sample size calculation ***and continuation of the trial as planned*** or recalculating sample size based on the effect size estimations of the interim analysis ***and based on conditional power assessments*** 2. Investigating which ***active*** treatment arm, if applicable, should be stopped after the interim analysis 3. […] […] Rejection of a null hypothesis will be possible at the interim analysis if the p-values with respect to the null hypothesis and all logically related hypotheses fall below α_1, where α_1 is determined by the O'Brien-	

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<table>
<tr><th>Change</th><th>CTP sections affected</th><th>Original Text
(CTP for the USA
v1.0 / 07.03.2024)</th><th>Revised Text
(CTP for the USA
v2.0 / 30.07.2024)</th><th>Rationale</th></tr>
<tr><td></td><td>Section 9.3.3 - Interim Analysis</td><td>Fleming α-spending function.

Table newly added:
<table><tr><th>Stage</th><th>Information Rate</th><th>Critical value</th><th>Significance level (one-sided)</th><th>Alpha spent</th></tr><tr><td>1</td><td>0,6</td><td>2,572</td><td>0,0051</td><td>0,0051</td></tr><tr><td>2</td><td>1</td><td>1.992</td><td>0,0232</td><td>0,0250</td></tr></table>N/A</td><td>Fleming α-spending function.
The corresponding overall values are shown in the following table.

The displayed critical value is on the z-value scale (calculated from the spent alpha levels). The critical value after the first part derived from the global Dunnett test with 3 active groups and with the corresponding α-level of 0.0051 (degrees of freedom [df]=188, correlation=0.5 due to the equal groups sizes) is 2.945.
A null hypothesis will be rejected at the final stage if the values of the respective inverse normal combination functions belonging to the null and all logically related hypotheses exceed the critical value on the z-scale.</td><td></td></tr>
</table>

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	Section 9.3.3 - Interim Analysis	[…] A null hypothesis will be rejected at the final stage if the values of the respective inverse normal combination functions belonging to the null and all logically related hypotheses fall below c, where c is determined by the O'Brien-Fleming α-spending function. […]	[…] ~~***A null hypothesis will be rejected at the final stage if the values of the respective inverse normal combination functions belonging to the null and all logically related hypotheses fall below c, where c is determined by the O'Brien Fleming α spending function.***~~ […] ***Further details regarding the interim analysis will be described in the respective SAP for the interim analysis (iSAP).***	
Harmonisation in regard to the question which of the treatment arms could possibly be stopped as a result of the interim analysis.	Synopsis - Statistical Analysis Section 9.3.3 - Interim Analysis	[…] • Investigating which treatment arm, if applicable, should be stopped after the IA […]	[…] • Investigating which ***active*** treatment arm, if applicable, should be stopped after the IA […]	To avoid any inconsistencies throughout the protocol the wording regarding the possible stop of at least one active treatment arm has been harmonised.

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Change in calculation of the daily ANMS-GCSI total score and the weekly average of the ANMS CGSI-DD total score.	Section 9.3.8 - Missing values	[…] The daily ANMS GCSI-DD total score is the sum of the scores (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) divided by 5. If one symptom score is missing for a day, the ANMS GCSI-DD total score is the sum of the scores of the available 4 core symptom items divided by 4. If more than one symptom score is missing for a day, the ANMS GCSI-DD total score is regarded as missing for this day.	[…] The daily ANMS GCSI-DD total score is the sum of the scores (0-4) of the 5 core symptom items (nausea, early satiety, postprandial fullness, upper abdominal pain, number of vomiting episodes) divided by 5. ~~***If one symptom score is missing for a day, the ANMS GCSI-DD total score is the sum of the scores of the available 4 core symptom items divided by 4.***~~ If ~~***more than***~~ ***at least*** one symptom score is missing for a day, the ANMS GCSI-DD total score is regarded as missing for this day. ***In accordance with the original planning and in accordance with the calculation as provided in the eCRF (for details refer to section 6.4.12.1), the daily ANMS GCSI-DD total score will also be calculated if only 4 of the 5 core symptoms has been assessed on the respective day. In this case the ANMS GCSI-DD***	In agreement with the recommendations concerning the handling of missing data regarding the primary efficacy endpoint, and the handling of days with intake of rescue medication, as given as given in FDA's comments 9 and 10, the rules for handling of missing data have been adapted. However, the originally planned procedure to exclude days with the intake of rescue medication will also be maintained as a sensitivity analysis.

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	Section 9.3.8 - Missing values	In case that rescue medication (preferably dimenhydrinate, alternatively cyclizine or meclozine) has been taken on a given day, the score values for the ANMS GCSI-DD will be set to missing for this day and the rule for missing values will be applied for the weekly average. If the documentation of the intake of dimenhydrinate (or cyclizine or meclozine) is missing, then no intake will be assumed. The ANMS GCSI-DD total symptom score for a week is the average of the daily total scores over the 7 days of a week.	***total score will be the sum of remaining 4 core symptom items divided by 4. Such an analysis of the weekly average score of the ANMS GCSI DD based on this calculation will be performed as a sensitivity analysis.*** ~~***In case that rescue medication (preferably dimenhydrinate, alternatively cyclizine or meclozine) has been taken on a given day, the score values for the ANMS GCSI-DD will be set to missing for this day and the rule for missing values will be applied for the weekly average. If the documentation of the intake of dimenhydrinate (or cyclizine or meclozine) is missing, then no intake will be assumed.***~~ The ANMS GCSI-DD total symptom score for a week is the average of the daily total scores over the 7 days of a week ***regardless the use of rescue medication.***	

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	Section 9.3.8 - Missing values	In case of 1 or 2 missing daily total scores the ANMS GCSI-DD total score within a week, the mean will be calculated based on the 5 or 6 available values, respectively. If data of less than 5 days are available (> 2 days missing) the ANMS GCSI-DD total score will not be evaluable for the respective week.	In case of 1 or 2 missing daily total scores the ANMS GCSI-DD total score within a week, the mean will be calculated based on the 5 or 6 available values, respectively. If data of less than 5 days are available (> 2 days missing) the ANMS GCSI-DD total score will not be evaluable for the respective week. ***For the purpose of a sensitivity analysis the following rule will be applied: In case that rescue medication (preferably dimen-hydrinate, alternatively cycli-zine or meclozine) has been taken on a given day, the score values for the ANMS GCSI-DD will be set to missing for this day and the rule for missing values will be applied for the weekly average. If the documentation of the intake of dimenhydrinate (or cyclizine or meclozine) is missing, then no intake will be assumed.***	

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	Section 9.3.8 - Missing values	No imputation methods for other missing values are planned to be performed.	No imputation methods for other missing values are planned to be performed.	
For the training of patients on the ePROM, the importance of avoiding missing data was emphasized more strongly.	Section 6.4.12 - Patient Questionnaires and Patient's diary (ePROM)	[…] At SCR 2 (V1) the investigator or delegated person will thoroughly train patients on how to use the ePROM. In addition, patients via their web-access, will have access to a completion guide in local language throughout the trial. […]	[…] At SCR 2 (V1) the investigator or delegated person ***is required to~~will~~*** thoroughly train patients ***in the proper ~~on how to~~*** use ***of*** the ePROM, ***emphasizing the importance of avoiding missing data***. In addition, patients via their web-access, will have access to a completion guide in local language throughout the trial. […]	To further underline the importance to avoid missing data, the wording regarding the corresponding training of patients has been updated, as recommended by the FDA,
Specification regarding the calculation of the ANMS-GCSI-DD average weekly total symptom score in the eCRF	Section 6.4.12.1 - The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom	[…] The ANMS GCSI-DD average weekly total symptom score for the last week prior to BSL (V2) which is relevant for patient's eligibility to participate in the double-blind treatment phase will also be calculated automatically and displayed in the eCRF (=average of the daily total symptom scores over the 7 days	[…] The ANMS GCSI-DD average weekly total symptom score for the last week prior to BSL (V2) which is relevant for patient's eligibility to participate in the double-blind treatment phase will also be calculated automatically and displayed in the eCRF (=average of the daily total symptom scores over the 7 days	To emphasize that the practical conduct of the study does not change compared to the initial planning, the description of the calculation of the ANMS-GCSI-DD average weekly total symptom score in the eCRF has been specified in more detail.

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	Index-Daily Diary	prior to BSL, excluding days with intake of rescue medication (preferably dimenhydrinate, alternatively cyclizine or meclozine) or missing days. […] Note: The ANMS GCSI-DD average weekly total symptom score will only be displayed in the eCRF, if at least 5 reliable daily total symptom scores per week are available.	prior to BSL, excluding days with intake of rescue medication (preferably dimenhydrinate, alternatively cyclizine or meclozine) or missing days. ***For the calculation in the eCRF, the mean ANMS GCSI score for a single day will only be calculated if a patient has documented at least 4 of 5 core symptom items (nausea, early feeling of fullness, postprandial feeling of fullness, upper abdominal pain, number of vomiting episodes) for that day.*** […] Note: The ANMS GCSI-DD average weekly total symptom score will only be displayed in the eCRF, if at least 5 reliable daily total symptom scores per week are available. ***Regarding the statistical analysis, the daily sum score of the ANMS GCSI-DDs and the ANMS GCSI-DD average weekly total symptom scores will be recalculated***	

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	Section 6.4.12.1 - The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary		***according to the rules as described in section 9.3.8.***	
The use of rescue medication for more than 2 times a week has been defined as an intercurrent event and a corresponding secondary estimand has been introduced.	Synopsis – Estimands	For the evaluation of the primary objective of the trial, four different estimands will be defined. All four estimands will use the patient level weekly average of the ANMS GCSI-DD total score as endpoint. […]	For the evaluation of the primary objective of the trial, ***~~four~~five*** different estimands will be defined. All ***~~four~~five*** estimands will use the patient level weekly average of the ANMS GCSI-DD total score as endpoint. […] ***Secondary estimand III*** ***The third secondary estimand will be a without-rescue-medication estimand comparing the groups while the subjects took the IMP without using rescue medication for more than***	As days with intake of rescue medication will no longer be excluded from the weekly average of the ANMS-GCSI-DD total score for the primary analysis and based on the FDA's comment 10 the intake of rescue medication has now been introduced as an intercurrent event. Correspondingly an additional secondary estimand has been defined to properly analyse the impact of the use of rescue medication, if taken more than

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	Synopsis - Estimands		***2 days per week. The relevant ICE is the use of rescue medication on more than 2 days per week regardless of other ICEs.***	2 times a week as foreseen according to the protocol.
		Secondary estimand III: The third secondary estimand will be again a hypothetical estimand comparing the treatment groups in a hypothetical population where no major protocol deviations or relevant ICEs would appear that is, it will be a population as described for the per-protocol set (PPS).	Secondary estimand ***~~III~~IV***: The ***~~third~~fourth*** secondary estimand will be again a hypothetical estimand comparing the treatment groups in a hypothetical population where no major protocol deviations or relevant ICEs would appear that is, it will be a population as described for the per-protocol set (PPS).	
	Section 9.3.1.2 - Definition of Estimands	[…] For the evaluation of the primary objective of the trial, four different estimands will be defined: a primary and 3 secondary estimands. All four estimands will use the patient level weekly average of the ANMS GCSI-DD total	[…] For the evaluation of the primary objective of the trial, ***~~four~~five*** different estimands will be defined: a primary and ~~3~~4 secondary estimands. All ***~~four~~five*** estimands will use the patient level weekly average of the ANMS GCSI-DD total	

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	Section 9.3.1.2 - Definition of Estimands	symptom score as subject level endpoint. […]	symptom score as subject level endpoint. […] ***<u>Secondary estimand III</u>*** ***The third secondary estimand will be a without-rescue-medication estimand comparing the groups while the subjects took the IMP without using rescue medication for more than 2 days per week. The relevant ICE is the use of rescue medication on more than 2 days per week regardless of other ICEs.*** ***The main estimator will be derived from an MMRM while missing values will be imputed by LOCF. A secondary estimator will use the MMRM model without explicit imputation as described for the primary estimator of the primary estimand.***	

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	Section 9.3.1.2 - Definition of Estimands	Secondary estimand III The third secondary estimand will be again a hypothetical estimand comparing the treatment groups in a hypothetical population where no major protocol deviations or relevant ICE would appear that is, it will be a population as described for the PPS. […]	Secondary estimand ~~***III***~~***IV*** The ~~***third***~~***fourth*** secondary estimand will be again a hypothetical estimand comparing the treatment groups in a hypothetical population where no major protocol deviations or relevant ICE would appear that is, it will be a population as described for the PPS. […]	
Integration of time-by-treatment interaction in the MMRM model.	Section 9.3.1.2 - Definition of Estimands	Primary estimand […] The primary estimator will be an adequate contrast of a mixed model repeated measure procedure (MMRM). The model will include the fixed factors treatment group, time, and type of gastroparesis (idiopathic, diabetic) and time as repeated effect. […]	Primary estimand […] The primary estimator will be an adequate contrast of a mixed model repeated measure procedure (MMRM). The model will include the fixed factors treatment group, time, ***treatment-by-time interaction,*** and type of gastroparesis (idiopathic, diabetic) and time as repeated effect. […]	As proposed in comment 13 of the FDA the MMRM model has been adapted, including the time-by-treatment interaction
Introduction of an ANCOVA model to derive the main estimator.	Section 9.3.1.2 - Definition of Estimands	Secondary estimand I [„„]	Secondary estimand I […]	With comment 14 the FDA recommended to use an analysis of covariance

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	Section 9.3.1.2 - Definition of Estimands	The main estimator will be derived from an MMRM using only the baseline (BSL, V2) and EOT (V6) as timepoints. A secondary estimator will be similar to the primary estimator but using all time points in the model. […]	The main estimator will be derived from an ***analysis of covariance (ANCOVA) model using the fixed factors treatment group, type of gastroparesis, and Baseline ANMS GCSI-DD average weekly total symptom score as covariate.*** A secondary estimator will be similar to the primary estimator but using all time points in the model. […]	(ANCOVA) model instead of an MMRM to derive the main estimator, as only one post-baseline measurement is used and no repeated post-baseline measures. Following this comment an ANCOVA model has now been introduced.
Transition of the IMP's primary packaging from blisters to bottles with childproof caps.	Section 5.1 - General	[…] The IMP provided must be used only in the context of this clinical trial. Each individual medication kit and blister card containing the IMP is marked with a unique medication kit number (see section 5.3 for details). […]	[…] The IMP provided must be used only in the context of this clinical trial. Each individual medication kit and blister card ***or bottle with a childproof cap*** containing the IMP is marked with a unique medication kit number (see section 5.3 for details). […]	For logistical and safety reasons, the sponsor has decided to change the primary packaging of the IMP from blister packs to bottles with childproof caps with the next following packaging campaign
	Section 5.3 - Packaging and Dispensing	[…] Each medication kit contains an IMP supply for 4 weeks (4 weekly blister cards) as well as a contingency reserve of one week (1 weekly blister card extra). Each blister card with 21	[…] Each medication kit contains an IMP supply for 4 weeks ***~~(4 weekly blister cards)~~*** as well as a contingency reserve of one week ***~~(1 weekly blister card extra)~~, either packed in blister cards***	

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		naronapride/placebo tablets is sufficient for one week of treatment (three IMP/placebo tablets are needed for one day of treatment).	with 21 naronapride/placebo tablets ***per blister, each ~~is~~*** sufficient for one week of treatment (three IMP/placebo tablets are needed for one day of treatment) ***or packed in a bottle with a childproof cap, containing a total of 105 tablets***.	
	Section 5.5 – Drug Accountability	[…] The patient will be asked to return the dispensed IMP (regardless of the content of the blisters) at the interim visits (ITR 2 [V4] and ITR 3 [V5], only), and at the EOT/WD visit (V6), respectively. The number of tablets administered will be confirmed by counting the returned unused medication and empty blister cards returned at these visits. All trial medication as well as empty blister cards will finally be shipped to the drug supplier at the end of the trial for destruction, if not otherwise specified and agreed with the sponsor.	[…] The patient will be asked to return the dispensed IMP (regardless of the content of the blisters ***or bottles, respectively***) at the interim visits (ITR 2 [V4] and ITR 3 [V5], only), and at the EOT/WD visit (V6), respectively. The number of tablets administered will be confirmed by counting the returned unused medication and empty blister cards ***or bottles*** returned at these visits. All trial medication as well as empty blister cards ***or bottles*** will finally be shipped to the drug supplier at the end of the trial for destruction, if not otherwise specified and agreed with the sponsor.	

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	Section 6.4.13 - Recording of compliance	[…] The person responsible for the trial medication calculates the amount of used IMP by counting the unused IMP based on returned IMPs (blister cards and tablets) at ITR 2 (V4) and ITR 3 (V5) (interim count) and at EOT/WD (V6) (final count). […]	[…] The person responsible for the trial medication calculates the amount of used IMP by counting the unused IMP based on returned IMPs (blister cards ***or bottles*** and tablets) at ITR 2 (V4) and ITR 3 (V5) (interim count) and at EOT/WD (V6) (final count). […]	
EC #16 and #24 have been changed for clarity reasons. Thereby Carmenthin® and Iberogast® have been deleted as tradenames because Menthacarin and STW5 are not available under these tradenames in the USA.	Synopsis - Exclusion Criteria and Section 3.1.2 - Exclusion Criteria	16. History of more than mild stroke or coronary artery disease	16. History of ***~~more than mild stroke or coronary artery disease~~moderate or severe cardiovascular or cerebrovascular events:*** • ***Stroke with sequelae that affect mobility or neuropsychiatric sequelae interfering with study aims,*** • ***Brainstem infarction with potential influence on autonomic nervous system,*** • ***Coronary heart disease (CHD) grade II-IV according to the Canadian Cardiovascular Society***	Some exclusion criteria have been further specified in order to better describe the subject population suitable for trial participation or to avoid any misunderstanding and thus to facilitate the selection of suitable subjects.

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			grading of angina pectoris. Grade I (angina with strenuous or rapid or prolonged exertion) or asymptomatic CHD is allowed, • ***Myocardial infarction.***	
	Synopsis - Exclusion Criteria and Section 3.1.2 - Exclusion Criteria	24. Use of any over-the-counter medication within two weeks prior to BSL (visit 2) that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin [Carmenthin®], STW5 [Iberogast®]),	24. Use of any over-the-counter medication within two weeks prior to BSL (visit 2) that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin ***~~[Carmenthin®]~~***, STW5***~~[Iberogast®]~~***),	
	Section 5.6.1 - Concomitant Medication	Table 5.3 […] Any over the counter medication that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin [Carmenthin®], STW5 [Iberogast®]) […]	Table 5.3 […] Any over the counter medication that may alter gastrointestinal motility (including but not limited to loperamide, menthacarin ***~~[Carmenthin®]~~***, STW5 ***~~[Iberogast®]~~***) […]	

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Addition of temperature in degrees Fahrenheit	Section 5.2 - Characteri-sation of IMP	Table 5.1 and Table 5.2 For clinical trial use only! Keep out of reach of children! Do not store above 25°C.	Table 5.1 and Table 5.2 For clinical trial use only! Keep out of reach of children! Do not store above 25°C ***(77°F)***.	To correspond to the temperature unit commonly used in the USA, the storage temperature for the IMP has been supplemented by the specification in degrees Fahrenheit
Adaptation of expected end of trial	Synopsis - Trial Duration Section 3.4 – Project Time Schedule	[…] Estimated end: 1st quarter 2025 (last patient last visit [LPLV]) […] The estimated recruitment period is 24 months and planned to start in the second quarter of 2022 ("first patient first visit", FPFV). Trial duration including screening, treatment and follow-up phase for each participant is 18-22 weeks. The clinical trial is expected to end in the fourth quarter of 2024. The trial end is defined as "last patient last visit" (LPLV).	[…] Estimated end: ~~***1st***~~***2nd*** quarter 2025 (last patient last visit [LPLV]) […] The ***originally*** estimated recruitment period ***was*** 24 months and ***was*** planned to start in the second quarter of 2022 ("first patient first visit", FPFV). Trial duration including screening, treatment and follow-up phase for each participant is 18-22 weeks. ***According to the current progress of recruitment, the*** clinical trial is expected to end in the ***second quarter of 2025***. The trial end is defined as "last patient last visit" (LPLV).	The expected end of trial has been adjusted to the current expectations.

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Specification and adaptation regarding the description of the DSMB's responsibilities	Section 7.5 - DSMB and IDMC	[…] In order not to disseminate unblinded data and to ensure that all staff involved in the conduct and analysis of the trial remains blinded to the results of the DSMB reviews, only the members of the DSMB and an unblinded statistician will have access to these data. Before the first DSMB meeting, a Data Safety Analysis Plan will be prepared and approved by the sponsor. The DSMB will receive blinded data according to the DSMB charter. Only in case the DSMB determines that it needs access to unblinded data for their decision, the unblinded statistician will unblind the data by electronically matching the random code of the respective patient(s) requested by the DSMB. He/she will confidentially provide the unblinded data only to the DSMB members.	[…] In order not to disseminate unblinded data and to ensure that all staff involved in the conduct and analysis of the trial remains blinded to the results of the DSMB reviews, only the members of the DSMB ***including ~~and an~~the*** unblinded statistician ***(DSMB Chairperson)*** will have access to these data. ***~~Before the first DSMB meeting, a Data Safety Analysis Plan will be prepared and approved by the sponsor.~~*** The DSMB will receive blinded data ***~~according to the DSMB charter~~as further detailed in the DSMB charter for their review***. Only in case the DSMB determines that it needs access to unblinded data for their decision, the unblinded statistician will unblind the data by electronically matching the random code of the respective patient(s) requested by the DSMB. He/she will confidentially provide the	With the adaptation of Section 7.5 in relation to the interim analysis by the IDMC, the wording in relation to the DSMB has also been revised for the sake of precision.

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	Section 7.5 - DSMB and IDMC		unblinded data only to the DSMB members.	
Deletion of previous Appendix A	Appendix A Appendix B Appendix C	Appendix A: Country Coordinating Investigators Signature Page (template)	Previous Appendix A: N/A Numbering of subsequent Appendices have been updated accordingly: New Appendix A: Previous Appendix B (Investigator Signature Page [template]) New Appendix B: Previous Appendix C (List of Changes with Amendments)	As being not required in the USA, previous Appendix A (Country Coordinating Investigators Signature Page (template)) has been deleted.
Change of CRO's study mailbox address	Section 7.2.2.1 - Investigator's Reporting Responsibili-ties for SAEs and Section 12.4 - Serious Breaches	PPD	PPD	Due to organizational changes, the address of the CRO's study mailbox needs to be updated

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Change	CTP sections affected	Original Text (CTP for the USA v1.0 / 07.03.2024)	Revised Text (CTP for the USA v2.0 / 30.07.2024)	Rationale
Minor editorial changes	All sections	N/A	N/A	In addition to the above-mentioned changes, some minor corrections such as spelling errors, errors in punctuation, etc. have been done.

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List of Changes with Integrated Clinical Trial Protocol – Final Version 3.0 / 07.10.2024

The following overview outlines the changes implemented with the Integrated Clinical Trial Protocol (version 3.0 / 07.10.2024) based on the Integrated Clinical Trial Protocol (version 2.0 / 21.12.2023) and incorporating all changes included in the Clinical Trial Protocol for the USA(version 1.0 / 07.03.2024 and version 2.0 / 30.07.2024) and the Local Protocol Addendum 01 for US (version 1.0 / 23.01.2014) as well in the Clinical Trial Protocol for Australia (version 1.0 / 18.03.2024) for the NAT-19/GPX trial, which became necessary to harmonize the clinical study protocol across all countries involved in this clinical trial.

Regarding the individual changes that have been made to the protocol with the first and second version of the Clinical Trial Protocol for the USA and the first version of the Clinical Trial Protocol for Australia, please refer to the respective Lists of Changes above.

Beside these changes the length between the first and the second screening visit has been extended from up to 14 days to up to 28 days to provide more flexibility in case there is the need to perform an upper gastrointestinal endoscopy (UGE) and/or an abdominal sonography/computer tomography (CT)/magnetic resonance imaging (MRI) to exclude any mechanic and/or anatomical obstructions, stenosis, structural diseases, or gastric ulcers. Moreover, for EU/EEA countries reporting responsibilities of the Sponsor for SUSARs have been updated to meet the requirements of the CTR (Regulation (EU) No. 536/2014).

The individual changes that have been made are detailed in the table below. The additions are being highlighted in ***bold italics***. Text which has been deleted is ~~crossed out~~).

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<table>
<tr><th>Change</th><th>CTP sections affected</th><th>Original Text
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v2.0 / 30.07.2024;
CTP for AUS
v. 1.0 / 18.03.2024;
Integrated CTP
v2.0 / 21.12.2023)</th><th>Revised Text
(Integrated CTP
v3.0 / 07.10.2024)</th><th>Rationale</th></tr>
<tr><td>Information about drug screening for US patients enrolled into the NAT-19/GPX trial was integrated.</td><td>Synopsis - Exclusion Criteria
and
Section 3.1.2 – Exclusion Criteria

Flow Chart</td><td>38. ...
For the USA only:
39.Positive urine drug screening at SCR 2 (visit 1) and at BSL (visit 2) except when the result is consistent with current prescribed medication history at the discretion of the investigator (considering the permitted drugs and dosages).

<table>
<tr><th colspan="3">Visit (V) No.
Visit Name</th><th>0
SCR 1</th><th>1
SC R 2</th><th>2
BS L</th><th>3-5
ITR 1-3</th><th>6
EOT /WD</th><th>7
FU/E OS</th></tr>
<tr><td rowspan="2">Labs</td><td rowspan="2">Local lab:</td><td>Urinalysis (local)</td><td></td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr>
<tr><td>Blood coagulation [6]</td><td>•</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>...</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td><td>

<table>
<tr><th colspan="3">Visit (V) No.
Visit Name</th><th>0
SCR 1</th><th>1
SC R 2</th><th>2
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EOT /WD</th><th>7
FU/E OS</th></tr>
<tr><td rowspan="3">Labs</td><td rowspan="3">Local lab:</td><td>Urinalysis (local)</td><td></td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr>
<tr><td>Blood coagulation [6]</td><td>•</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Drug screening (urine dipstick test)[#]</td><td></td><td>•</td><td>•</td><td></td><td></td><td></td></tr>
<tr><td>...</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
For the USA only.</td><td>Information about drug screening was added due to incorporation of Local Protocol Addendum 01 for US (version 1.0 / 23.01.2014); applicable for the USA only.</td></tr>
</table>

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	Section 6.4.6.1 – Safety Assessments	The following parameters will be analysed in the **local laboratory**: • Urine: o Urine strip test (Combur-9-Test; provided by the central laboratory) at SCR 2 (V1), BSL (V2), at every interim visit (ITR V1 [V3] - ITR V3 [V5]), at EOT/WD visit (V6) and EOS/FU visit (V7): protein, glucose, ketone, bilirubin, blood, urobilinogen, pH, nitrite, leucocytes. o Urine hCG pregnancy tests (provided by the central laboratory) at SCR 1 (V0), BSL (V2) at every interim visit (ITR 1 [V3] - ITR 3 [V5]),	The following parameters will be analysed in the **local laboratory**: • Urine: o Urine strip test (Combur-9-Test; provided by the central laboratory) at SCR 2 (V1), BSL (V2), at every interim visit (ITR V1 [V3] - ITR V3 [V5]), at EOT/WD visit (V6) and EOS/FU visit (V7): protein, glucose, ketone, bilirubin, blood, urobilinogen, pH, nitrite, leucocytes. o ***For the USA only*: Urine strip test for drug screening (provided by the central laboratory) at SCR 2 (V1) and BSL (V2).**	

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		EOT/WD visit (V6) and EOS/FU visit (V7) for female patients of childbearing potential. In all cases, freshly obtained midstream urine will be used to measure the urine parameters.	o Urine hCG pregnancy tests (provided by the central laboratory) at SCR 1 (V0), BSL (V2) at every interim visit (ITR 1 [V3] - ITR 3 [V5]), EOT/WD visit (V6) and EOS/FU visit (V7) for female patients of childbearing potential. In all cases, freshly obtained midstream urine will be used to measure the urine parameters.	
Duration between the first and the second screening visit has been extended from up to 14 days to up to 28 days.	Synopsis – Trial Design	[..] The overall trial duration for the individual participant is estimated to be 18-22 weeks from screening to end of follow-up with maximum 8 visits. **Screening Phase (Up to 6 Weeks):**	[..] The overall trial duration for the individual participant is estimated to be 18-~~22~~**24** weeks from screening to end of follow-up with maximum 8 visits. **Screening Phase (Up to ~~6~~8 Weeks):**	Duration was adapted to provide more flexibility in case there is the need to perform an upper gastrointestinal endoscopy (UGE) and/or an abdominal sonography/computer tomography (CT)/magnetic resonance imaging (MRI) to

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	Synopsis – Treatment duration	During the 2 to 6 weeks lasting screening phase, the presence and persistence of trial-entry criteria will be evaluated. [..] The treatment duration per participant is 12 weeks. The trial duration per participant is 18-22 weeks with a total of 8 trial visits: **Screening phase (SCR)**: Up to 6 weeks Visit 0: SCR 1 (Up to 14 days prior to SCR 2) Visit 1: SCR 2 (14 – 28 days prior to BSL (visit 2)	During the 2 to ~~6~~**8** weeks lasting screening phase, the presence and persistence of trial-entry criteria will be evaluated. [..] The treatment duration per participant is 12 weeks. The trial duration per participant is 18-~~22~~**24** weeks with a total of 8 trial visits: **Screening phase (SCR)**: Up to ~~6~~**8** weeks Visit 0: SCR 1 (Up to ~~14~~**28** days prior to SCR 2) Visit 1: SCR 2 (14 – 28 days prior to BSL (visit 2)	exclude any mechanic and/or anatomical obstructions, stenosis, structural diseases, or gastric ulcers

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<tr><td></td><td>Flow Chart</td><td>FLOW CHART
<table><tr><td></td><td>ACTIVITIES</td><td></td></tr><tr><td></td><td>Phase</td><td>Screening (SCR)*</td></tr><tr><td></td><td>Visit (V) No.
Visit Name</td><td>0
SCR 1</td><td>1
SCR 2</td></tr><tr><td></td><td>Day</td><td>Up to 14 days prior to SCR 2</td><td>14 -28 days prior to BSL</td></tr></table></td><td>FLOW·CHART¶
<table><tr><td></td><td>ACTIVITIES¤</td><td></td></tr><tr><td></td><td>Phase¤</td><td>Screening·(SCR)*¤</td></tr><tr><td></td><td>Visit·(V)·No.¶
Visit·Name¤</td><td>0¶
SCR·1¤</td><td>1¶
SCR·2¤</td></tr><tr><td></td><td>Day¤</td><td>Up·to·~~14~~·28·days·prior·to·SCR·2¤</td><td>14·-28·days·prior·to·BSL¤</td></tr></table></td><td></td></tr>
<tr><td></td><td>Section 3.4 – Project Time Schedule</td><td>Trial duration including screening, treatment and follow-up phase for each participant is 18-22 weeks.</td><td>Trial duration including screening, treatment and follow-up phase for each participant is 18-~~22~~24 weeks.</td><td></td></tr>
<tr><td></td><td>Section 4 – Trial Design</td><td>The overall trial duration for the individual participant is estimated to be 18-22 weeks from screening to end of follow-up with maximum 8 visits.</td><td>The overall trial duration for the individual participant is estimated to be 18-~~22~~24 weeks from screening to end of follow-up with maximum 8 visits.</td><td></td></tr>
<tr><td></td><td>Section 6.1 – Time Sequence and Frames</td><td>The trial period for an individual patient consists of a 2 to 6 weeks lasting screening phase, a double-blind treatment phase of 12 weeks and a 4-week follow-up phase.</td><td>The trial period for an individual patient consists of a 2 to ~~6~~8 weeks lasting screening phase, a double-blind treatment phase of 12 weeks and a 4-week follow-up phase.</td><td></td></tr>
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(Integrated CTP
v3.0 / 07.10.2024)</th><th>Rationale</th></tr>
<tr><td></td><td>Section 6.2 – Overview of Time Sequence</td><td>Table 6-1: Visit schedule
<table><tr><th>Visit</th><th>Visit no.</th><th>Day no.</th><th>V</th></tr><tr><td>SCR visit 1[1)]</td><td>V0</td><td>Up to 14 days prior to SCR visit 2</td><td></td></tr><tr><td>SCR visit 2[1)]</td><td>V1</td><td>14 – 28 days[2)] prior to BSL visit</td><td></td></tr></table>
The trial will begin with a screening visit 1 (SCR 1; V0), which should take place within up to 42 days prior to the BSL visit (V2) or up to 14 days prior to the second SCR visit (SCR 2; V1), respectively.</td><td>Table 6-1: Visit schedule
<table><tr><th>Visit</th><th>Visit no.</th><th>Day no.</th></tr><tr><td>SCR visit 1[1)]</td><td>V0</td><td>Up to ~~14~~ ~~28~~ days prior to SCR visit 2</td></tr><tr><td>SCR visit 2[1)]</td><td>V1</td><td>14 – ~~28~~ days[2)] prior to BSL visit</td></tr></table>
The trial will begin with a screening visit 1 (SCR 1; V0), which should take place within up to ~~42~~56 days prior to the BSL visit (V2) or up to ~~14~~28 days prior to the second SCR visit (SCR 2; V1), respectively.</td><td></td></tr>
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	Section 6.4.8 – Upper gastrointestinal endoscopy (UGE)	An UGE within the first two weeks of the screening phase that serves to exclude any mechanic and/or anatomical obstructions, stenosis, structural diseases, or gastric ulcers needs to be performed only in case that no previous UGE has been performed in the 12 months prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.	An UGE within ~~the first two weeks of the screening~~ **phase*28 days prior to the second screening visit (SCR 2, V1)*** that serves to exclude any mechanic and/or anatomical obstructions, stenosis, structural diseases, or gastric ulcers needs to be performed only in case that no previous UGE has been performed in the 12 months prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.	

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	Section 6.4.9 – Abdominal Sonography or MRI or CT	To exclude intestinal stenosis an abdominal sonography, MRI, or CT (CT to be performed only, if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK]) during the first two weeks of the screening phase needs to be performed only, if no previous MRI/CT imaging or sonography has been done in the last 12 month prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.	To exclude intestinal stenosis an abdominal sonography, MRI, or CT (CT to be performed only, if part of the clinical routine in the respective participating country; e.g., not applicable for Germany, Switzerland and United Kingdom [UK]) ~~during the first two weeks of the screening phase~~ ***within 28 days prior to the second screening visit (SCR 2, V1)*** needs to be performed only, if no previous MRI/CT imaging or sonography has been done in the last 12 month prior to SCR 1 (V0) and provided that no relevant changes in patient's disease status occurred since that time.	
Total blood volume was aligned with volumes defined in the central lab manuals.	Section 6.4.6 – Laboratory Parameters	For central and local laboratory assessments a total blood volume of approximately 90 to 100 mL is to be taken during the complete trial. If necessary, for safety	For central and local laboratory assessments a total blood volume of approximately ~~90~~**84** to ~~100~~**101** mL is to be taken during the complete trial. If necessary, for	In the former Clinical Trial Protocol, version 2.0, total blood volume taken during the trial was given on average. This was specified in the

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		reasons, additional blood samples may be taken.	safety reasons, additional blood samples may be taken.	current version by stating the exact range resulting from volumes per visit defined in the central lab manuals.
SUSAR reporting by the Sponsor/CRO to Ethics Committees was removed for EU/EEA countries.	Section 7.2.2.2 –Reporting Responsibili-ties of the Sponsor	SUSARs for the EU/European Economic Area (EEA) countries will be reported to EudraVigilance. The Sponsor is responsible for reporting SUSARs to EudraVigilance. Reporting SUSARs to Ethics Committees in the EU/EEA countries is contractually delegated to the coordinating CRO. A SUSAR report has to be approved by the Sponsor's Drug Safety Officer before sending it to EudraVigilance and the Ethics Committee(s).	***For the EU/European Economic Area (EEA) countries and the USA the Sponsor is responsible to report SUSARs electronically to the European Medicines Agency (EMA) (EudraVigilance) and to the Food and Drug Administration (FDA, via an US Agent), respectively.*** ~~SUSARs for the EU/European Economic Area (EEA) countries will be reported to EudraVigilance. The Sponsor is responsible for reporting SUSARs to EudraVigilance. Reporting SUSARs to Ethics Committees in the EU/EEA countries is contractually delegated to the coordinating CRO.~~ A SUSAR report has to be approved by the	According to CTR (Regulation (EU) No. 536/2014) SUSAR reporting to EudraVigilance is sufficient for EU/EEA countries (reporting by Sponsor/CRO to ethics committees is only necessary for non-EU member states). In addition, the sponsor responsibilities for reporting SUSARs in the USA have been supplemented.

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Change	**CTP sections affected**	**Original Text (CTP for the USA v2.0 / 30.07.2024; CTP for AUS v. 1.0 / 18.03.2024; Integrated CTP v2.0 / 21.12.2023)**	**Revised Text (Integrated CTP v3.0 / 07.10.2024)**	**Rationale**
		SUSAR reporting to the CAs outside of the European Union will be performed by the CRO according to national/local requirements.	Sponsor's Drug Safety ~~Officer~~***Manager*** before sending it to EudraVigilance and ***FDA*** ~~the Ethics Committee(s)~~. SUSAR reporting to ***Independent Ethics Committees/Institutional Review Boards (IRBs) and*** the CAs outside of the European Union will be performed by the CRO according to national/local requirements.	
IRB supplemented	Table of Abbreviations Section 8.2.1 – Termination of the Whole Trial	N/A […] • Withdrawal of Independent Ethics Committee's (IEC's) approval of the study, […]	***IRB*** | ***Institutional Review Board*** […] • Withdrawal of Independent Ethics Committee's (IEC's)***/Institutional Review***	With the revision of the Sponsor/CRO's reporting requirements in relation to SUSAR reporting including the introduction of Institutional Review Boards (IRBs) as counterpart of Independent Ethics Committees in the USA, the IRBs were also supplemented in other places for consistency reasons

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	Section 10 – Protocol Amendment(s) Section 13.2 – Independent Ethics Committees/In-stitutional	[…] … and must be submitted to the relevant IECs and CAs (where applicable) for application for a favourable opinion/approval prior to being initiated, … […] Administrative or technical changes, which do not affect the health interests of the patients, do not require a new vote by the IEC or a new informed consent from the patients already included in the trial. Section Title: Independent Ethics Committees and National Competent Authorities	***Board's (IRB's)*** approval of the study, […] […] … and must be submitted to the relevant IECs***/IRBs*** and CAs (where applicable) for application for a favourable opinion/approval prior to being initiated, … […] Administrative or technical changes, which do not affect the health interests of the patients, do not require a new vote by the IEC***/IRB*** or a new informed consent from the patients already included in the trial. Section Title: Independent Ethics Committees***/Institutional Review***	

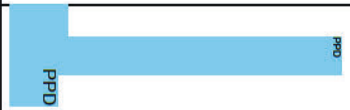
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Change	**CTP sections affected**	**Original Text (CTP for the USA v2.0 / 30.07.2024; CTP for AUS v. 1.0 / 18.03.2024; Integrated CTP v2.0 / 21.12.2023)**	**Revised Text (Integrated CTP v3.0 / 07.10.2024)**	**Rationale**
	Review Boards and National Competent Authorities	In conformity with the national guidelines and the GCP provisions, the trial protocol, the patient information/informed consent form and any other document given to the patient has been submitted to an IEC before the start of the trial. The clinical trial in each of the participating countries will only start after having received an initial ethics approval.	***Boards*** and National Competent Authorities In conformity with the national guidelines and the GCP provisions, the trial protocol, the patient information/informed consent form and any other document given to the patient has been submitted to an IEC***/IRB*** before the start of the trial. The clinical trial in each of the participating countries will only start after having received an initial ethics approval.	
Addition of the information that bottles with childproof caps are only used in the USA	Section 5.1 – General	The IMP provided must be used only in the context of this clinical trial. Each individual medication kit and […] blister card or bottle with a childproof cap, […]	The IMP provided must be used only in the context of this clinical trial. Each individual medication kit and […] blister card or bottle with a childproof cap **(for the USA only)**, […]	As bottles with a childproof cap are only used as primary packaging for IMPs in the USA, a corresponding note has been added for clarity reasons.

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Change	CTP sections affected	Original Text (CTP for the USA v2.0 / 30.07.2024; CTP for AUS v. 1.0 / 18.03.2024; Integrated CTP v2.0 / 21.12.2023)	Revised Text (Integrated CTP v3.0 / 07.10.2024)	Rationale
	Section 5.3 – Packaging and Dispensing	Each medication kit contains an IMP supply for 4 weeks as well as a contingency reserve of one week, either packed in blister cards with 21 naronapride/placebo tablets per blister, each sufficient for one week of treatment (three IMP/placebo tablets are needed for one day of treatment) or packed in a bottle with a childproof cap, containing a total of 105 tablets.	Each medication kit contains an IMP supply for 4 weeks as well as a contingency reserve of one week, either packed in blister cards with 21 naronapride/placebo tablets per blister, each sufficient for one week of treatment (three IMP/placebo tablets are needed for one day of treatment) or packed in a bottle with a childproof cap ***(for the USA only)***, containing a total of 105 tablets.	
	Section 5.5 – Drug Accountability	[…] The patient will be asked to return the dispensed IMP (regardless of the content of the blisters or bottles, respectively) at the interim visits (ITR 2 [V4] and ITR 3 [V5], only), and at the EOT/WD visit (V6), respectively. […]	[…] The patient will be asked to return the dispensed IMP (regardless of the content of the blisters or bottles ***(for the USA only)***, respectively) at the interim visits (ITR 2 [V4] and ITR 3 [V5], only), and at the EOT/WD visit (V6), respectively. […]	

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	Section 6.4.13 – Recording of Compliance	The person responsible for the trial medication calculates the amount of used IMP by counting the unused IMP based on returned IMPs (blister cards or bottles and tablets) at ITR 2 (V4) and ITR 3 (V5) (interim count) and at EOT/WD (V6) (final count). This count will be checked versus the patient's documentation of IMP intake. If necessary, discrepancies should be clarified, if possible.	The person responsible for the trial medication calculates the amount of used IMP by counting the unused IMP based on returned IMPs (blister cards or bottles ***(for the USA only)*** and tablets) at ITR 2 (V4) and ITR 3 (V5) (interim count) and at EOT/WD (V6) (final count). This count will be checked versus the patient's documentation of IMP intake. If necessary, discrepancies should be clarified, if possible.	
Change of CRO's study mailbox address	Section 7.2.2.1 - Investigator's Reporting Responsibili-ties for SAEs and Section 12.4 - Serious Breaches			Due to organizational changes, the address of the CRO's study mailbox needs to be updated

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Update of Title page, Synopsis	Title Page Synopsis	Current protocol version	Beside the current protocol version all previous (local) protocol versions have been listed. In addition, all country-specific trial IDs have been included in the synopsis	For harmonization of different protocol versions, relevant protocol sections were amended accordingly.
Update of Signature page(s)	Protocol Signatures	PM at CRO: PPD Biostatistician: PPD	PM at CRO: PPD Biostatistician: PPD	To enable CRF Part 11-compliant signatures, the signature page had to be divided into several pages. For administrative reasons the CRO's Project Manager and the responsible Biostatistician have changed
Minor editorial changes	All sections	N/A	N/A	In addition to the above-mentioned changes, some minor corrections such as spelling errors, errors in punctuation, etc. have been done.

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