CLINICAL TRIAL PROTOCOL

A Phase III randomized, multicenter non-inferiority study to evaluate the efficacy and safety of shorter Benznidazole regimens compared to the standard regimen to treat adult patients with Chronic Chagas disease in indeterminate form or with mild cardiac progression.

Abbreviated title	NuestroBen- New scheme for Benznidazole Treatment
Name of product(s)	Abarax®, Benznidazole; N-benzyl-2-nitro-1H-imidazole-1-acetamide
Drug Class	Nitroimidazole
Phase	Phase III
Indication	Chronic Chagas Disease in indeterminate form or with mild cardiac progression
Protocol Number	*NuestroBen-2020*
Sponsor	ELEA-Phoenix (Argentina) Drugs for Neglected Diseases initiative (DNDi), Chemin Camille-Vidart 15, 1202 Geneva, Switzerland (Phone: +41 22 906 9230) (Bolivia)
Manufacturer	Laboratorio ELEA-Phoenix, Buenos Aires, Argentina

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Protocol Version / Date	*Version 4.0 dated 24 April 2025*

1. PROTOCOL SUMMARY

Protocol Title	A Phase III randomized, multicenter non-inferiority study to evaluate the efficacy and safety of shorter Benznidazole regimens compared to the standard regimen to treat adult patients with chronic Chagas disease in indeterminate form or with mild cardiac progression
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Background Information and Trial Rationale	Chagas disease (CD), caused by the parasite *Trypanosoma cruzi* (T. cruzi), is one of the most neglected diseases in the world. In Latin America, Chagas disease occurs endemically in 21 countries, with an estimated 70 million people at risk of infection. The current standard of care for CD — nifurtimox (NFX) and benznidazole (BZN) — has significant limitations, including a long treatment duration (60 days), safety concerns, and challenges related to tolerability and adherence. Current treatment regimens and dose intervals are result of decades of treatments, which were conducted to several patients, and with very limited comparisons. Data from recently completed studies suggest that there is potential to optimize BZN treatment regimens. Between 2011 and 2013, a Phase II proof of concept clinical study was conducted in Bolivia testing E1224, a broad spectrum antifungal triazole compound, and BZN, sponsored by the Drugs for Neglected Diseases initiative (DNDi) (CH-E1224-001; NCT01489228) in adult patients with the indeterminate chronic form of Chagas disease. A standard of care arm (BZN 300 mg daily for 8 weeks) was included in this study. Parasites were undetectable in all patients treated with BZN for 8 weeks (standard of care arm) after 2 weeks of treatment. The primary efficacy endpoint was the sustained parasitological response measured by quantitative polymerase chain reaction (PCR) at the end of 12 months of follow-up. In 81% of these patients, eradication of the parasite was sustained during the 12 months after treatment. Likewise, the safety data of the study indicated that 10-20% of the patients treated with BZN did not complete the treatment according to the conditions of drug use, mainly due to adverse drug reactions (headaches, nausea, pruritus, peripheral neuropathy, and hypersensitivity) and the long duration of treatment. Data from recent population pharmacokinetic studies in adults suggested that the current BZN dose regimen (5-7 mg/kg day, 60 days) may cause overexposure in most patients. On the contrary, based on modelling (DNDi-MORU), dose simulations suggested that at a daily dose of 2.5 mg/kg BID of BZN, plasma levels of BZN would be well within the recommended target range for most patients in 4 to 8 weeks regimens. In addition, there is the potential to evaluate fixed-dose regimens for adults, rather than mg/kg

	calculations, facilitating use and potentially improving adherence in expanding treatment for T. cruzi infection. Similarly, several controlled observational studies, with daily doses of BZN 5 mg/kg for 30 or 60 days, demonstrated that the progression of heart disease with serological conversion (no detection of specific IgG antibodies against *T. cruzi* sometime after treatment in patients with previously positive serology before treatment) was reduced by up to 60% in children and 30% in adults. Different publications have demonstrated antiparasitic efficacy in treatments lasting 30 and 60 days, as well as in incomplete treatments lasting 10 days. After the DNDi-CH-E1224-001 study, a new Phase II study sponsored by DNDi (BENDITA study, CH-E1224-003; NCT03378661) was conducted in Bolivia to evaluate a new regimen of BZN as monotherapy and in combination with E1224. BENDITA was a Phase II, randomized, double-blind, placebo-controlled study run in Bolivia between 2016 and 2018 to determine the efficacy and safety of different BZN regimens as monotherapy, or in combination with E1224, in the sustained reduction and elimination of the T. cruzi parasite in adults with the indeterminate chronic form of Chagas disease. The primary efficacy endpoint was the parasitological response by serial PCR at the end of treatment, maintained until six months after treatment. Secondary efficacy analyses with same parameters were performed at 12 months. In total, 518 patients were screened. Of those, 210 were randomized, divided into 30 patients in each of the seven groups: BZN 300 mg daily for a) 8 weeks, b) 4 weeks or c) 2 weeks; d) BZN 150 mg daily for 8 weeks e) BZN 150 mg daily for 4 weeks; f) BZN 150 mg daily for 4 weeks in combination with E1224 300 mg weekly; g) placebos. Two hundred and two (202) patients completed the study. The primary efficacy analysis on the intention-to-treat population showed that 89.3% maintained elimination of the parasite at 6 months after treatment with BZN 300 mg for 8 and 4 weeks; 82.8% maintained elimination after treatment with a 300 mg dose for 2 weeks; 83.3%, with a treatment of BZN 150 mg for 4 weeks; and 85.2%, with BZN 300 mg for 4 weeks in combination with E1224, compared with 3.3% in the placebo group.

	According to safety results, there was a high rate of adherence to treatment in all groups. Six patients (20%) discontinued in BZN 300 mg treatment for 8 weeks arm; 1 patient (3.3%), in BZN 300 mg for 4 weeks arm; none in BZN 300 mg for 2 weeks arm; 1 (3.3%) discontinued in BZN 150 mg for 4 weeks arm; 3 (10%) in BZN150 mg for 4 weeks in combination with E1224 arm, and 4 (13.3%) in BZN 300 mg in combination with E1224 weekly arm. Most adverse events were mild to moderate, with only 6 patients presenting serious adverse events (SAEs): 2 patients (6.7%) in BZN 300 mg 8 weeks; 1 patient (3.3%) in both the BZN 300 mg 4 weeks and the BZN 150 mg 4 weeks treatment in combination with E1224 arm; 2 patients (6.7%) in BZN 300 mg in combination with E1224 weekly. No SAEs were reported in the 2-week BZN 300 mg or 4-week BZN 150 mg arms. The results showed that a short course of treatment with BZN maintained the parasitological response effectively and with good tolerability in participants included in this study until the end of follow-up, which suggests that it could be a new treatment approach for adults with T. cruzi infection. However, BENDITA study was not designed to compare arms, but to evaluate the efficacy of each arm. The NuestroBen study aims to evaluate the efficacy and safety of a 2-week BZN 300 mg regimen and a 4-week BZN 300 mg regimen, compared to the standard treatment of BZN 300 mg for 8 weeks (~ 60 days). The standard BZN regimen is currently indicated as a first-line treatment for adult patients with the indeterminate chronic form T. cruzi infection and mild chronic Chagas disease (mild organ involvement). BZN has a well-characterized safety profile, with adverse effects primarily influenced by dose and treatment duration. The most common AEs include gastrointestinal symptoms (nausea, vomiting, abdominal pain), dermatological reactions (rash, pruritus, photosensitivity), and neurological effects (headache, dizziness, paresthesia). These are generally mild to moderate and manageable with medical supervision. Serious but rare adverse events (SAEs) include severe cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS), bone marrow suppression (neutropenia, thrombocytopenia, anemia), and peripheral neuropathy. In most cases, symptoms resolve upon treatment

	discontinuation. Carcinogenic effect is not known in humans, as described in the IB and in the FDA label, since long-term carcinogenicity studies for benznidazole have not been performed. Nitroimidazoles, which have similar chemical structures to benznidazole have been reported to be carcinogenic in mice and rats. It is not known whether benznidazole is associated with carcinogenicity in humans. The risk-benefit balance remains favourable when used according to approved guidelines. Based on these risks, the protocol includes specific safety measures for monitoring liver function, hematology and dermatological reactions to ensure early detection and appropriate management. Currently, one of the reasons for the low rate of treatment coverage for people with Chagas disease is the moderate or low adherence to the treatment scheme, its safety profile primarily in adult population, and the long duration of treatment (60 days). If safety and/or efficacy benefits are confirmed, this shortened therapy may be a promising alternative BZN regimen for treatment since it would reduce duration and increase adherence to treatment, improving the overall treatment risk/benefit profile for this disease, and significantly increasing treatment access and coverage.

Trial Objectives	General Objective: • To assess the efficacy and safety of 2-week and 4-week regimens of BZN (300 mg daily), compared to the standard treatment of BZN (300 mg daily) for 8 weeks, in terms of reducing and eliminating the T. cruzi parasite in adults in the chronic phase of Chagas disease with the indeterminate form or mild cardiac progression. Primary Objective: • To demonstrate non-inferiority of treatment with BZN 300 mg daily for 2 weeks and 4 weeks (100 mg TID) compared to the standard treatment of BZN 300 mg daily for 8 weeks (100 mg TID), and among arms, in individuals in the chronic phase of Chagas disease with the indeterminate form or mild cardiac involvement, establishing the proportion of participants with sustained clearance of parasitemia according to the results of qualitative PCR tests from the end of treatment, and up to 12 months of follow-up from the end of treatment. Secondary Objectives: • To describe the proportion of participants with sustained clearance of parasitemia according to the results of qualitative PCR tests at 1, 4, 6 and 8 months of follow-up from the end of treatment. • To evaluate the safety profile of treatment with the 2-week and 4-week regimens of BZN (300 mg daily) according to anamnesis, physical examination and laboratory tests compared to the standard treatment with BZN of 300 mg daily for 8 weeks, and among them. • To evaluate the incidence of Serious Adverse Events (SAEs) and/or adverse events that lead to the interruption of treatment with the 2-week and 4-week regimens of BZN at (300 mg daily) compared to the standard treatment with BZN 300 mg daily for 8 weeks, and between the 2-week and 4-week arms. • To describe the adherence of participants to the treatment in each study arm

	Exploratory Objective: • To evaluate the efficacy of 2-week and 4-week regimens of BZN (300 mg daily) based on non-conventional anti-T. cruzi antibody levels (including Multicruzi among others potential biomarkers identified) from baseline over time
Trial Endpoints	**Efficacy evaluation primary endpoint** • The primary endpoint is negative serial qualitative PCR results from the end of treatment with sustained parasitemia clearance through to the end of 12 months' follow-up period from the end of treatment. To assess the non-inferiority efficacy among study groups, parasitological response will be evaluated and compared. Parasitological response for each participant will be determined by negative serial qualitative PCR results. For efficacy evaluations, the completion of each treatment arm will be defined according to the duration of the assigned treatment, that is, on day 14 of the 2-week regimen of BZN at 300 mg, on day 28 of the 4-week regimen of BZN at 300 mg, and on day 56 of the standard treatment of 300 mg daily for 8 weeks. **Safety and efficacy evaluation secondary endpoints** • The secondary efficacy endpoint is defined as negative serial qualitative PCR results from the end of treatment with sustained parasitemia clearance at 1, 4, 6 and 8-month follow-up from the end of treatment. • The secondary safety endpoints are: o Incidence and severity of adverse events (clinical and laboratory measurements) o Incidence of SAEs, Adverse Events of Special Interest (AESIs) and/or adverse events that cause treatment interruption. Safety will be assessed via routine monitoring of adverse events, evaluation of hematology and blood chemistry values, regular measurement of vital signs and physical examinations at specified visits (in accordance with the

study schedule).

Exploratory endpoint:

- The exploratory endpoint is defined as the decline in anti-Chagas antibody levels over time using non-conventional antibody tests (including Multicruzi among others potential biomarkers identified) from baseline, at 6 and at 12-month follow-up.

Primary Objective & Clinical Research Question	**Primary Endpoint / Estimands**
Primary Objective: To demonstrate non-inferiority of treatment with BZN 300 mg daily for 2 weeks and 4 weeks (100 mg TID) compared to the standard treatment of BZN 300 mg daily for 8 weeks (100 mg TID). **Clinical Research Question:** Are the regimens of 2-week and 4-week of BZN (300 mg daily) non inferior to the 8-weeks regimen in terms of reducing and eliminating the *T. cruzi*	• **Population**[1]**:** Adults in the chronic phase of Chagas disease with the indeterminate form or mild cardiac progression who were included and randomized to the study and with one positive result of qPCR before treatment, with at least one dose of study drug and with, at least, one PCR qualitative result during follow-up. • **Treatment condition:** BZN 300mg oral daily (100 TID) for 2 weeks, 4 weeks and 8 weeks. • **Endpoint:** The primary endpoint is negative serial qualitative PCR results from the end of treatment with sustained clearance of parasitemia until the end of 12 months' follow-up from the end of treatment. For efficacy evaluations, the completion of each treatment arm will be defined

[1] For analysis purposes, the following populations are defined and described in further in the Statistical Analysis Plan of the trial: **Intention-to-treat**: all included participants who were randomized in the study (positive PCR at baseline); **Per protocol:** All participants who completed the study without significant protocol deviations. Those who presented a positive PCR before exclusion period during follow-up will be considered treatment failure; **Safety population:** All participants who received at least one of the study drug dose

parasite in adults in the chronic phase of Chagas disease with the indeterminate form or mild cardiac progression? Additionally, if both 2-weeks and 4-weeks regimens are non-inferior to the 8-weeks regimen, is 2-weeks regimen non inferior to the 4-weeks regimen?	according to the duration of the assigned treatment, that is, on day 14 of the 2-week regimen of BZN at 300 mg, on day 28 of the 4-week regimen of BZN at 300 mg, and on day 56 of the standard treatment of 300 mg daily for 8 weeks. • **Summary measure:** Difference between the arms in proportions of patients with sustained clearance of parasitemia until the end of 12 months' follow-up from the end of treatment. • **Intercurrent events:** In case of early discontinuation (before treatment end) or taking a different antiparasitic, this will be considered a treatment failure in ITT analysis and will not be included in PP analysis.
Secondary objectives	**Secondary Endpoints**
To describe the proportion of participants with sustained clearance of parasitemia according to the results of qualitative PCR tests at 1, 4, 6 and 8 months of follow-up from the end of treatment.	• **Population:** Adults in the chronic phase of Chagas disease with the indeterminate form or mild cardiac progression with at least 01 dose of study drug and qualitative PCR results during the follow-up. • **Endpoints:** The secondary endpoint is negative serial qualitative PCR results from the end of treatment with sustained clearance of parasitemia at 1, 4, 6 and 8 months' follow-up from the end of treatment. • **Summary measure:** Proportion of patients with sustained clearance of parasitemia at 1, 4, 6 and 8 months' follow-up from the end of treatment.

		• **Intercurrent events:** In case of early discontinuation (before treatment end) or taking a different antiparasitic, this will be considered a treatment failure in ITT analysis and will not be included in PP analysis.
	To evaluate the safety profile of both treatment regimens (2-week and 4-week BZN300 mg daily) compared to standard treatment regimen with BZN of 300 mg daily for 8 weeks, and among them.	• **Population:** Adults in the chronic phase of Chagas disease with the indeterminate form or mild cardiac progression with at least 01 dose of study drug; • **Endpoints**: Incidence and severity of adverse events (clinical and laboratory measurements); • **Summary measure:** Proportion of participants with an endpoint. Safety will be assessed via routine monitoring of adverse events, evaluation of hematology and blood chemistry values, regular measurements of vital signs and physical examinations at specified visits throughout the whole study. • **Intercurrent events:** In case of treatment interruption due to AE(s) or any other reason without a rescue therapy and use of prohibited drugs, a treatment strategy defined in this protocol will be conducted.
	To evaluate the incidence of Serious Adverse Events (SAEs) and/or adverse events leading to treatment interruption with the 2-week and 4-week BZN regimens at 300 mg	• **Population:** Adults in the chronic phase of Chagas disease with the indeterminate form or mild cardiac progression with at least 01 dose of study drug; • **Endpoints:** Incidence of SAEs, Adverse Events of Special Interest (AESIs) and/or adverse events that lead to treatment interruption;

	daily, compared to the standard treatment regimen of BZN at 300 mg daily for 8 weeks.	Safety will be assessed via routine monitoring of adverse events/SAEs/AESIs throughout the whole study. • **Summary measure:** Proportion of patients with an endpoint • **Intercurrent events:** In case of treatment interruption due to AE(s) or any other reason without a rescue therapy and use of prohibited drugs, a treatment strategy defined in this protocol will be conducted.
Trial Design	A Phase III, open-label, prospective, randomized controlled, multicenter, non-inferiority study to compare the efficacy of a 2-week and 4-week BZN 300 mg/day treatment with the standard treatment of BZN 300 mg dose/day for 8 weeks (100 mg TID in all arms). The trial will be conducted in six different sites in Argentina and two sites in Bolivia. The total number of sites may increase depending on the recruitment rate.	
Primary criteria to enter the study Inclusion Exclusion	The study aims to enrol a total of approximately 540 participants. **Inclusion criteria** Participants are eligible to be included in the clinical trial only if all of the following criteria apply: ● Signed informed consent form; ● Between ≥18 and ≤60 years old at the time of signing the informed consent ● Body weight within ≥ 50 kg to ≤ 95 kg; ● Confirmation of the diagnosis of *T. cruzi* infection by	

	conventional serology (a minimum of two tests must be reactive); • Serial qualitative PCR (one blood sample divided in three DNA extractions, at least one of which must be positive); • Women of childbearing potential must have a negative pregnancy test at inclusion, must not be breastfeeding, and must use a highly effective contraceptive method during treatment and for 35 days after the last dose, • Ability to comply with all protocol specific tests and visits; • Having a permanent address; • ECG criteria: Heart rate: 50 -100 bpm or isolate sinus bradycardia from 41 to 59 beats/min; QRS ≤120 msec and QTc* ≥350 msec and ≤450 msec at screening or following findings belonging to non-severe chagasic cardiomyopathy: incomplete right bundle branch block, left anterior fascicular block, first-degree atrioventricular block, low voltage. The included abnormalities are not exclusionary (all those that are defined as mild chagasic cardiomyopathy); (*Note: QTc will be corrected using the Fridericia's formula) • Normal or minimal structural changes in echocardiogram (left ventricular diastolic diameter (LVDD) <= 55 mm, diastolic dysfunction, absence of Microaneurysm or tip aneurysm, absence of hypo or generalized akinesia, absence of Systolic dysfunction (low fractional shortening and ejection fraction), and/or absence of mural thrombus); • Not presenting signs or symptoms of moderate- severe chronic cardiac and/or digestive forms of Chagas disease (criteria detailed in the Study Manual and specific SOP); • No prior history of mental disorders or suicidal tendencies; • No history of acute or chronic diseases that, in the Investigator's judgment, may interfere with the assessment of the efficacy or safety of the investigational product (such as

	acute infections, immunosuppressive conditions, or liver or kidney diseases that have required treatment); • No formal indication to refrain from taking BZN (contraindication, according to the Summary of Product Characteristics – SmPC); • No prior history of hypersensitivity, allergy, or serious adverse reactions to any of the nitroimidazole compounds (including BNZ) and/or its components/excipients; • Have not previously undergone antiparasitic treatment for *T. cruzi* infection; • No prior history of drug abuse or alcoholism (please consult Study Manual); • Not suffering from any disease or condition that prevents participants from consuming oral medication. **Exclusion criteria** Participants are excluded from the clinical trial if any of the following criteria apply: • Participant pregnant or intending to become pregnant during treatment and within 35 days of the last dose of study treatment • Signs or symptoms of the moderate to severe chronic cardiac and/or digestive form of Chagas disease, or any ECG/ echocardiographic findings not included in the inclusion criteria; • History of cardiomyopathy, heart failure, or severe ventricular arrhythmia; • History of digestive surgery potentially related to Chagas Disease or megacolon / mega-esophagus; • Acute or chronic disease that, in the Investigator's judgment, may interfere with the assessment of the efficacy or safety of

	the investigational product (such as acute infection, history of immunosuppressive conditions, liver or kidney disease that has required treatment and blood dyscrasias); • Laboratory test values that are considered clinically significant and/or exceed Grade 2 limits according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, as determined by medical judgment • Disease or clinical condition that prevents participants from consuming oral medication; • Participants with a contraindication (known hypersensitivity) to any of the nitroimidazole compounds, e.g., metronidazole; • Participants with a history of non-pharmacological severe allergies; allergic rash, asthma; • Participants with a history of pharmacological severe allergies, severe intolerance, sensitivity or photosensitivity to any drug; • Concomitant use and/or consumption of allopurinol, antimicrobial and antiparasitic agents, herbal medicines, dietary supplements and energy drinks; . • Use of alcohol or products containing propylene glycol during treatment and up to 5 days thereafter • Participants who have taken disulfiram within the last two weeks prior to inclusion • Scheduled surgery that may interfere with the conduct of the trial and/or with the treatment evaluation; • Inability to attend study visits, comply with treatment, and cooperate with study procedures; • Previous participation in a trial for the evaluation of the treatment of Chagas disease; • Simultaneous participation in another trial or within 3 months prior to screening for this trial (in accordance with national

	regulations) Participants suffering from a serious medical or psychiatric illness which, in the opinion of the investigator, increases the risk associated with study participation or that interferes with the interpretation of study results should not be included.
Study Duration	The total duration of the study from the start of recruitment to the end of follow-up is estimated up to 38 months. The duration of treatment will be two, four and eight weeks. Participants will be followed for 12 months from the end of assigned treatment. From the signing of the informed consent form, there will be a period of up to 30 days for the inclusion of the participant. In total, recruitment is expected to take place in a period of 26 months.
Study treatment	All 540 selected participants will be assigned to one of the following treatment groups: • Arm 1: 180 participants will receive as treatment: BZN (Abarax, 100 mg), 300 mg divided into three daily doses (100 mg every 08 hours) for 14 days. • Arm 2: 180 participants will receive as treatment: BZN (Abarax, 100 mg), 300 mg divided into three daily doses (100 mg every 08 hours) for 28 days. • Arm 3: 180 participants will receive as treatment: BZN (Abarax, 100 mg), 300 mg divided into three daily doses (100 mg every 8 hours) for 56 days. Each participant will be assigned a unique treatment number. BZN will be administered as 100 mg tablets contained in bottles specifically labeled for the study. Participants will be instructed to take the study medication in three daily doses every 8 hours (WINDOW+/-2HS) after a meal. At the inclusion visit, participants will receive enough medication to complete

	their treatment. They will be asked to bring any remaining medication at each study visit according to their assigned arm for review and treatment compliance, ensuring proper accountability of the medication. Participants will be provided with a diary and asked to record the exact date and time of each medication dose, which should be documented in the diary by the participant themselves or their caregiver. Based on the recommendations in the Benznidazole package insert and IB, participants will be advised to avoid alcohol consumption during treatment and for at least three days after completion. This precaution is due to the risk of a disulfiram-like reaction caused by the interaction between benznidazole and alcohol.
Statistics Sample size Randomization Summary of analysis	Efficacy endpoint Number and proportion of participants with sustained parasitemia clearance according to the results of qualitative PCR tests from the end of treatment, and up to 12 months of follow-up from the end of treatment. Treatments: ● Standard of care (SoC) treatment regimen: BZN 300 mg/day - 8 weeks (100 mg TID) ● New treatment regimens: - BZN 300 mg/day - 2 weeks (100 mg TID) - BZN 300 mg/day - 4 weeks (100 mg TID) The study is designed to establish the non-inferiority of the “new treatment regimens” compared to the “SoC treatment regimen” in terms of efficacy. Furthermore, the “new treatment regimens” are expected to reduce the incidence of ADRs and the rate of definitive discontinuation attributed to the study drug. Non-inferiority criteria The “new treatment regimen” will be considered non-inferior to the “current treatment regimen” if the upper limit of the 95% Bayesian credible confidence interval of the difference in the “Result” between both groups is

	≤ 20% (margin of non-inferiority). This is equivalent to the Bayesian posterior probability of inferiority Pr(SOC rate – new arm rate < 0.20) > 97.5%. **Sample Size Rationale** The study will enroll a total of 540 participants, with 180 participants per group. The sample size calculation follows a Bayesian non-inferiority approach, specifically Bayesian Assurance for Two Proportions with a Beta Prior for response rates. A prior distribution is assigned to the control group (BZN 300 mg for 8 weeks) to ensure robust statistical inference. The Bayesian assurance represents the unconditional probability of the trial demonstrating a predefined response rate difference, also known as Bayesian Power or the true probability of success. The statistical hypotheses include a significance level of 0.025 and expected response rates of 80% for the control group (BZN 8 weeks) and 75% for both the BZN 4-week and 2-week groups. The non-inferiority margin is set at -20%, with a Beta (5,2) prior distribution assigned to the expected response rate of the control arm. For a two-sample Bayesian non-inferiority test with a significance level of 2.5%, a non-inferiority margin of -0.2, and a treatment group response rate of 75%, a sample size of 180 participants per group provides a Bayesian assurance of 80%. This statistical approach ensures robustness and regulatory compliance while optimizing trial feasibility.
COVID-19 or pandemics contingency plan	The study will be adapted to national and local conditions and regulations for COVID-19 or any other similar situation. In situations where there are outbreaks, and in accordance with regulations that limit non-essential visits to health centers, or that affect the ability of participants to travel to follow-up sites, it may be necessary to postpone some visits to a later date. These postponed visits will be as close as possible to the original date, and always once the local authorities and conditions allow visits to the site without compromising participants safety. If there are prolonged restrictions on local travel (for example, by public transport), information on adverse events will be obtained from the participant by phone, while the collection of samples will be deferred. Prior to the beginning of the study, COVID-19/pandemics

	prevention measures will be reviewed with investigators and site staff, and information about COVID-19/pandemics will be provided to participants. Diagnostic kits and Personal Protective Equipment for staff and participants may be provided according to the needs of each site and the prevailing epidemic situation. Site staff will contact participants if a visit needs to be rescheduled.