CLINICAL INVESTIGATION PLAN

A randomized, placebo-controlled, double-blind, multicenter study to evaluate the efficacy of intranasal kinetic oscillation stimulation in the preventive treatment of chronic migraine

Study code:	PM007
Document code:	1002670E
Sponsor:	Chordate Medical AB Norgegatan 2 164 32 Kista, Sweden Visiting and delivery address from 01-Apr-2018: Chordate Medical AB c/o Regus Kistagången 20B 164 40 Kista, Sweden
Coordinating investigator:	[redacted] Department of Systems Neuroscience University Clinic Hamburg-Eppendorf (UKE) Martinistrasse 52 20246 Hamburg, Germany
Clinical investigation plan version and date:	Final 7.0, 14-Jun-2021
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This clinical investigation plan must be kept strictly confidential. Disclosure of the contents (in whole or part) to third parties is permissible only with written consent of Chordate Medical AB.

Revision chronology

- Original version: Version 1.0, dated 02-Nov-2017
- Version 2.0, dated 21-Feb-2018

  The following changes were included in Version 2.0 compared to Version 1.0:

  - The coordinating investigator was replaced.
- Version 3.0, dated 14-Mar-2018

  The following changes were included in Version 3.0 compared to Version 2.0

  - The assessment of the migraine disability assessment score (MIDAS) was removed;
  - The reporting processes of serious adverse events, pregnancies, and device deficiencies were changed from eCRF-based reporting to paper-based reporting and additional clarifications were added;
  - The documentation of headache and migraine days in the eCRF was clarified;
  - The pregnancy testing at Visit V1, V2, V3, V4, V5, V6, and V7 were removed;
  - The visiting and delivery address of Chordate changed starting on 01-Apr-2018 and was updated accordingly.
- Version 4.0, dated 06-Mar-2019

  The following changes were included in Version 4.0 compared to Version 3.0

  - The study design was changed to a 2-stage group-sequential design with one interim analysis that allows the premature termination of the study due to efficacy or futility or adaption of the sample size (described in detail in newly added Section 13.3; Sections 3 and 11.3.5 were updated accordingly);
  - Because of the newly introduced 2-stage group-sequential design, the sample size calculation was updated (Section 13.5) and the number of subjects to be enrolled was increased from previously 140 to 148 subjects (Sections 3, 11.3.1, and 11.3.5 were updated accordingly);
  - Another secondary performance endpoint was added (Sections 3 and 11.1.2): Mean change from Baseline in monthly headache days (mild, moderate and severe intensity) in 4-week performance assessment period (V3 to V7), and its analysis described in Sections 3 and 13.2.
- Version 5.0, dated -2019

  The following changes were included in Version 5.0 compared to Version 4.0

  - Finland was added as second study country;

- Addresses and names of involved sites were added;
- The documentation processes of patient data were changed from eCRF-based reporting to paper-based reporting

- Version 6.0-FIN, dated 05-Nov-2020

The following changes were included in Version 6.0-FIN compared to Version 5.0

- Addition of optional SARS-CoV-2 Test at treatment visits

- Version 7.0, dated 14-Jun-2021

The following changes were included in Version 7.0 compared to Version 6.0-FIN

- Safety part of the protocol was adapted according to EN ISO 14155:2020 and Regulation (EU) 2017/745

- Version 7.0, dated 14-Jun-2021

The following changes were included in Version 7.0 compared to Version 5.0

- Safety part of the protocol was adapted according to EN ISO 14155:2020 and Regulation (EU) 2017/745
- Addition of optional SARS-CoV-2 Test at treatment visits

Statement of compliance

This clinical investigation will be conducted in compliance with the clinical investigation plan (CIP) and the following regulatory requirements:

- International Standard ISO 14155:2011: Clinical investigation of medical devices for human subjects - Good clinical practice (GCP)
- Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, in its currently acknowledged revision
- Applicable sections of the national medical device law

By acting in accordance with this CIP, the investigators and the study site personnel fulfil the requirements of the International Standard ISO 14155:2011.

The clinical investigation will not commence until a favorable opinion from the respective ethics committees (ECs) and an authorization from the competent authority (CA) has been received. All additional requirements imposed by the ECs and/or the CA will be followed. Insurance coverage as required by national legislation has been taken out for this clinical investigation.

1 Table of contents

2 Abbreviations and definition of terms

ADE	Adverse device effect
AE	Adverse event
ANCOVA	Analysis of covariance
ASADE	Anticipated serious adverse device effect
BDRM	Blind data review meeting
CA	Competent authority
CGRP	Calcitonin gene-related peptide
CIP	Clinical investigation plan
CRO	Contract research organization
CSF	Cerebrospinal fluid
DMC	Data monitoring committee
EC	Ethics committee
eCRF	Electronic case report form
pCRF	Paper case report form
FAS	Full analysis set
GCP	Good Clinical Practice
GWAS	Genome-wide association studies
HIT-6	Headache impact test-6
IB	Investigator's Brochure
ICF	Informed consent form
ICHD	International Classification of Headache Disorders
ID	Identification
IFU	Instructions for Use
IHS	International Headache Society
KOS	Kinetic oscillation stimulation
MDD	Medical Device Directive
MedDRA	Medical Dictionary for Regulatory Activities
MSQ	Migraine-specific quality of life questionnaire
NSAIDs	Nonsteroidal anti-inflammatory drugs
PACAP-38	Pituitary adenylate cyclase-activating peptide
PGI-S	Patient global impression of severity
PP	Per protocol
PPS	Per protocol set
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDV	Source data verification
SOC	System organ class
TCC	Trigeminocervical complex
US	United States
USADE	Unanticipated serious adverse device effect
V	Visit

3 Synopsis and schedule of assessments

Study code

PM007

Title of the study

A randomized, placebo-controlled, double-blind, multicenter study to evaluate the efficacy of intranasal kinetic oscillation stimulation in the preventive treatment of chronic migraine

Principal investigators and study centers

5 centers in Germany and max. 6 centers in Finland

Coordinating investigator

[redacted] Department of Systems Neuroscience, University Clinic Hamburg-Eppendorf (UKE), Martinistrasse 52, 20246 Hamburg, Germany.

Duration of clinical investigation (planned)

The overall duration of the clinical investigation including enrollment and treatment of all subjects is anticipated to be about 3.5 years with an expected enrollment period of about36 months.

The duration of the clinical investigation for each participating subject is about 14 weeks.

Study objectives

Primary objective:

- To evaluate the effect of intranasal kinetic oscillation stimulation using the Chordate System S211 on monthly headache days with moderate to severe intensity.

Secondary objectives:

- To evaluate the effect of treatment with the Chordate System S211 on monthly migraine days, responder rate, use of abortive medication, health-related quality of life and disability, and patient's global impression of severity;
- To evaluate the incidence and severity of adverse events (AEs) and adverse device effects following treatment with the Chordate System S211.

Methodology

This is a randomized, placebo-controlled, double-blind, multicenter clinical investigation of a medical device. The study consists of a 4-week screening period, a 6-week treatment period (2 weeks run-in and a 4-week observation window to assess the treatment effect), and a 4-week follow-up period.

Subjects who provided written informed consent and are eligible for the study will be asked to complete a daily diary for 4 weeks during the screening period. In the diary the subjects will

record headache and migraine days, any changes in their health, and concomitant medications they may be using. The data collected in the diary during this screening period will be used as Baseline for the performance assessments.

Subjects who completed the screening period and continue to meet the eligibility criteria after review of diary entries by the investigator will be randomized (stratified by medication overuse) in a 1:1 ratio to receive either active or placebo treatment. The subjects will receive 6 treatments with the Chordate System S211 at weekly intervals at the site (Day 0 to 35; treatment Visit [V] 1 to 6) and continue to maintain a daily diary. One week after the last treatment, an end of treatment visit will be performed on Day 42 (V7).

After completion of the 6-week study treatment period (V1 to V7), subjects will be followed up for another 4 weeks. The final visit will be performed on Day 70, 5 weeks after the last study treatment. During the 4-week follow-up, the subjects will continue to complete a daily diary.

The study will be performed according to a 2-stage group-sequential design with one interim analysis that allows the premature termination of the study due to efficacy or futility or adaption of the sample size.

Medical device and application

Chordate System S211 consisting of the Chordate Controller, the Chordate Catheter and the Chordate Headband. The device stimulates the subject's nasal mucosa by means of mechanical pressure and vibrations at low frequencies. The treatment time will be 10 minutes in each cavity (a total of 20 minutes per treatment) at 85 Hz and 80 mbar.

Number of subjects planned

Approximately 148 subjects will be enrolled to achieve at least 132 subjects evaluable for the primary performance endpoint (assuming a drop-out rate of 10%), with 66 subjects receiving treatment with the Chordate System S211 and 66 subjects receiving treatment with the Chordate System S211 in placebo mode. If, during the conduct of the study, the drop-out rate proves to be higher than expected (>10%), enrollment will continue until at least 132 subjects were assessed for the primary endpoint. A group-sequential design with one interim analysis after approximately 50 subjects have completed the 6-week study treatment period will be used. It will allow the premature termination of the study due to efficacy or futility or adaption of the sample size.

Subject population

Subjects with diagnosed chronic migraine meeting all inclusion criteria and none of the exclusion criteria will be eligible for the study.

Inclusion criteria

1. The subject is legally competent, has been informed of the nature, the scope and the relevance of the study, voluntarily agrees to participation and the study's provisions, and has duly signed the informed consent form;
2. Male or female aged between 18 and 65 years (inclusive) at the time of providing informed consent;
3. Diagnosed as suffering from chronic migraine with or without aura (≥15 headache days per month for more than 3 months before screening including at least 8 migraine days) according to the International Headache Society classification (International Classification of Headache Disorders III beta);
4. Migraine onset before the age of 60 years;
5. Reported history of migraine for at least 1 year before screening;
6. Reported stable prophylactic migraine medication regimen, if any, during the 3 months prior to screening;
7. Able and willing to maintain current prophylactic migraine medication regimen (no change in type, frequency or dose) from screening to end of follow-up;
8. Women of childbearing potential must be willing to use highly effective contraceptive methods (failure rate <1% per year when used consistently and correctly) during the study.

Exclusion criteria

1. Unable to distinguish between migraine headaches and other headache types;
2. Treatment with Botox in the head/neck area within 4 months of the screening visit, or planned Botox treatment during the study;
3. Previous or ongoing treatment with an implanted stimulator or other implanted device in the head and/or neck;
4. Known pronounced anterior septal deviation, or other known relevant abnormality in the nasal cavity, including bacterial infection and wounds;
5. History of relevant sinus surgery, transsphenoidal surgery for pituitary or other lesions or cerebrospinal fluid rhinorrhea;
6. Fitted with a pacemaker/defibrillator;
7. Previously treated with therapeutic x-ray intervention in the facial region (that could have influenced the nasal mucosa);
8. Ongoing upper respiratory infection or malignancy in the nasal cavity;

9. History of regular nose bleeding (epistaxis), or concomitant condition or medication that could cause excessive bleeding including treatment with an anticoagulant;
10. Head injury or open wound that contraindicates use of the Chordate Headband;
11. Known allergy to polyvinylchloride, a material used in the Chordate Catheter, or medicinal liquid paraffin;
12. Concurrent condition or risk of non-compliance that, in the investigator's opinion, may affect the interpretation of performance or safety data or which otherwise contraindicates participation in a clinical investigation;
13. Pregnant and lactating women;
14. Participation in a clinical investigation within 3 months of enrolment or planned participation at any time during this clinical investigation;
15. Previous participation in this study;
16. Employees of the study site or the sponsor directly involved with the conduct of the study, or immediate family members of any such individuals;

Previous and concomitant treatments

Subjects using a stable regimen of prophylactic migraine medication will be required to maintain this regimen from screening to end of follow-up and no new prophylactic treatment may be initiated during that time. Subjects on unstable dose(s) of prophylactic migraine medication(s) 3 months prior to screening will not be enrolled.

Subjects can use their regular acute (abortive) migraine medication, when necessary, during the course of the clinical investigation. However, all such use must be documented in the study specific diary.

Criteria for evaluation

Performance endpoints

Primary performance endpoint:

- Mean change from Baseline (4-week screening period) in monthly headache days with moderate to severe intensity in 4-week performance assessment period (V3 to V7).

Secondary performance endpoints:

- Mean change from Baseline in monthly headache days with moderate to severe intensity in follow-up period;
- Mean change from Baseline in monthly migraine days;
- Mean change from Baseline in monthly headache days (mild, moderate and severe intensity) in 4-week performance assessment period (V3 to V7);

- Proportion of subjects with 30% or greater reduction in headache days of moderate to severe intensity;
- Proportion of subjects with 50% or greater reduction of headache days of moderate to severe intensity;
- Change in the use of acute (abortive) medication;
- Change in migraine-specific quality of life questionnaire (MSQ), headache impact test-6 (HIT-6), and patient global impression of severity (PGI-S).

Safety endpoint:

- Frequency, severity, device-relationship, and outcome of AEs.

Statistical methods

Primary performance analysis

The primary endpoint will be analyzed by an analysis of covariance with treatment, baseline number of headache days, and medication overuse as independent variables with the following null hypothesis:

$$H_{0:}\ \mu_{active} = \mu_{placebo} \quad \text{versus}$$

$$H_{1:}\ \mu_{active} \neq \mu_{placebo}$$

where μ is the mean change from Baseline (4-week screening period) in monthly headache days with moderate to severe intensity in 4-week performance assessment period (V3 to V7). If the data is not normally distributed, the van Elteren test will be used with medication overuse as strata. In addition, the number of monthly headache days and change from Baseline will be presented by descriptive statistics. A group-sequential design with O´Brien & Fleming alpha spending function with one interim analysis that allows the premature termination of the study due to efficacy or futility or adaption of the sample size will be used.

Secondary performance and safety analyses

All statistical tests for secondary performance endpoints are considered exploratory and no adjustment for multiplicity is made. All secondary endpoints will be evaluated for the performance assessment period and the follow-up period.

The mean change from Baseline in monthly headache days with moderate to severe intensity in the follow-up period, the mean change from Baseline in monthly migraine days (counting migraine days instead of headache days), and the mean change from Baseline in monthly headache days (mild, moderate and severe intensity) in 4-week performance assessment period (V3 to V7) will be analyzed as the primary performance endpoint.

The proportion of subjects with 30% or greater or 50% or greater reduction in headache days of moderate to severe intensity will be analyzed descriptively using frequency tables. The active and placebo arm will be compared using a Chi-square test. In case of a low number of subjects per group, the Fisher's exact test will be used.

The change in the monthly use of abortive medication will be presented by descriptive statistics.

The change in MSQ, HIT-6 and PGI-S will be presented by descriptive statistics. The change from Baseline will be tested using a Wilcoxon rank sum test.

Safety analyses

AEs will be presented by descriptive statistics showing the number and proportion of subjects with at least one AE overall and by system organ class and preferred term.

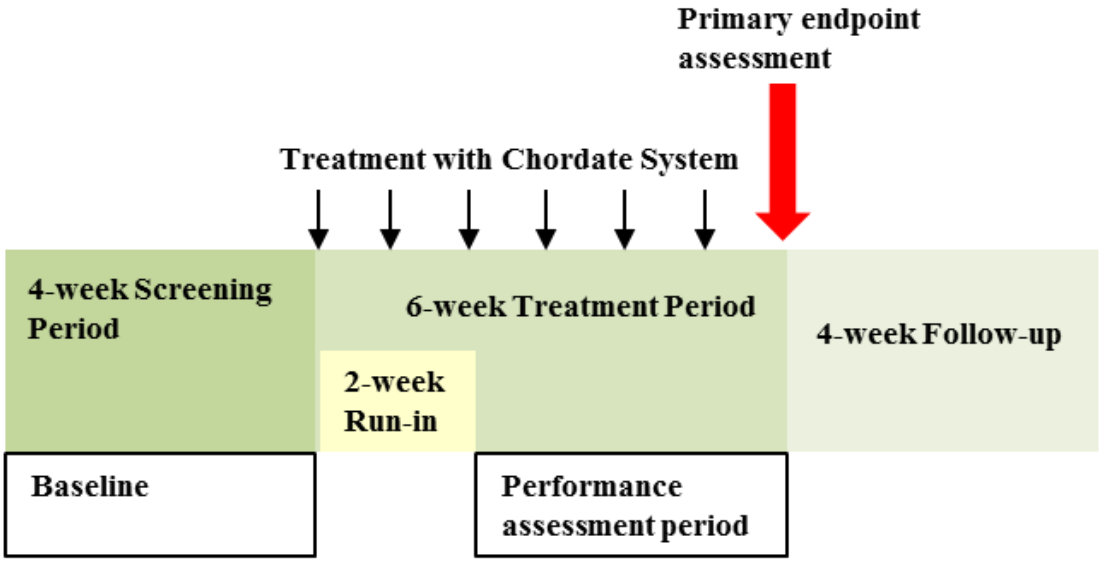
Schedule of assessments

	Screening	Visit 1 (V1)	Visit 2 (V2)	Visit 3 (V3)	Visit 4 (V4)	Visit 5 (V5)	Visit 6 (V6)	Visit 7 (V7)	FUP
	D -28 ±3d	**D0**	**D7 ±3d**	**D14 ±3d**	**D21 ±3d**	**D28 ±3d**	**D35 ±3d**	**D42 ±3d**	**D70 ±3d**
	W-4	**W0**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W10**
Informed consent	X								
Inclusion / exclusion criteria	X	X							
Demographics	X								
Medical and surgical history	X	X							
Physical examination	X								
Prior and concomitant medication	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X								X
Randomization		X							
HIT-6	X	X		X				X	X
MSQ	X	X		X				X	X
PGI-S	X	X		X				X	X
Treatment with Chordate System		X	X	X	X	X	X		
Documentation of adverse events		X[a]	X	X	X	X	X	X	X
SARS-CoV-2 Test[b]		X	X	X	X	X	X		
Reported in paper diary by subject									
Headache / migraine days	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X

[a] Adverse events will be documented during and after the first treatment with the Chordate System. Any changes in health prior to first treatment will be documented as medical history. [b] if required by site policy.

D = Day, d = days, FUP = Follow-up, HIT-6 = Headache Impact Test, MSQ = Migraine Specific Quality of life questionnaire, PGI-S = Patient Global Impression of Severity, V = Visit, W = Week.

Flow chart


Primary endpoint assessment
Treatment with Chordate System
4-week Screening Period
6-week Treatment Period
4-week Follow-up
2-week Run-in
Baseline
Performance assessment period

4 Addresses and responsibilities

Sponsor	Chordate Medical AB Norgegatan 2 164 32 Kista, Sweden	*Clinical Research Director:* Jan Hermansson Phone: +46 708467054

Visiting and delivery address from 01-Apr-2018:
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164 40 Kista, Sweden

Contract Research Organization	FGK Clinical Research GmbH Heimeranstr. 35 80339 Munich, Germany	*Project Manager* [redacted] *Medical Monitor* [redacted]

Coordinating investigator ***(Leiter der Klinischen Prüfung, according to German Medical Device Law)***	Department of Systems Neuroscience University Clinic Hamburg-Eppendorf (UKE) Martinistrasse 52 20246 Hamburg, Germany	[redacted] Phone: [redacted]

Center 01	Department of Systems Neuroscience, University Clinic Hamburg-Eppendorf (UKE), Martinistrasse 52, 20246 Hamburg, Germany	[redacted], neurologist
Center 02	Migräne-Klinik Königstein Verwaltungsgesellschaft mbH, Ölmühlweg 31, 61462 Königstein / Ts., Germany	[redacted], neurologist

Center 03	Closed	
Center 04	Neurologie- & Kopfschmerzzentrum, Leopoldstr. 59/II, 80802 München, Germany	[redacted], neurologist
Center 05	Universitätsmedizin Rostock, Zentrum für Nervenheilkunde, Klinik und Poliklinik für Neurologie, Gehlsheimer Str. 20, 18147 Rostock, Germany	[redacted], neurologist
Center 06	LEWIS Neurologie, Rotebühlstrasse 80 70178 Stuttgart, Germany	[redacted], neurologist
Center 81	Suomen Terveystalo Turku, Humalistonkatu 9-11, 20100 Turku, Finland	[redacted], neurologist
Center 82	Terveystalo Tampere, Rautatienkatu 27, 33100 Tampere, Finland	[redacted], neurologist
Center 83	Terveystalo Ruoholahti, Porkkalankatu 22, 00180 Helsinki, Finland	[redacted], neurologist
Center 84	Helsingin päänsärkykeskus / Aava Itäkeskus, Itäkatu 7, 00930 Helsinki, Finland	[redacted], neurologist

5 Background information and scientific rationale

Migraine is a chronic neurovascular disorder characterized by episodes of head pain that may be severe [1]. Associated features such as nausea, vomiting, and sensitivity to light, sound or movements are characteristic. Attacks usually last 4 to 72 hours when untreated. Approximately 30% of patients with migraine have an aura with focal neurological symptoms, usually visual, preceding the headache. The one-year prevalence is 11% in the United States (US) and Western Europe and the disorder is more common in women. At least 10% of patients have weekly attacks and the degree of disability during an attack is considered comparable with having quadriplegia.

Chronic migraine is defined as headache on ≥15 days/month out of which the headache must fulfill the International Headache Society (IHS) criteria for migraine on at least 8 days/month. The distinction between episodic (<15 headache days) and chronic (≥15 headache days) has been made as it is assumed that migraine occurring at a high frequency may involve additional pathophysiological features (e.g. a higher degree of neuronal sensitization) that may offer additional treatment targets. This assumption is supported by the observation that certain treatments (e.g. onabotulinumtoxin A) have only been proven effective in one of the two conditions.

The pathophysiology is incompletely understood. It is thought that an abnormal activation of the hypothalamus and the trigeminocervical complex form the basis of the severe attacks. The hypothalamus may play a significant role in the initiation of an attack as an abnormal activation can already be observed in the 1-2 days preceding the headache, causing the premonitory symptoms (yawning, mood changes etc.) of the attack, and lasting throughout the attack into the postdrome phase. With the initiation of the headache an activation of the trigeminocervical complex (TCC) within the brainstem as well as other key structures which include the thalamus and inhibitory areas such as the periaqueductal gray become involved [2].

During neuronal activation neuromodulatory peptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating peptide (PACAP-38) are released and increase nociceptive neuronal activity. These neuropeptides also induce dilation of cranial blood vessels, but the clinical relevance of this vascular response appears to play a minor role for the induction and maintenance of migraine attacks. However, the exact mechanism of the generation of pain is not known.

The higher prevalence in women compared to men has been linked to modulating effects of the sex hormones estrogen and progesterone [3]. A special form is menstrually-related migraine which is likely related to falling levels of sex hormones.

There is a certain degree of inheritance where the risk of developing migraine is about 80% if both parents suffer from migraine, and 60% if one parent has migraine. Genome-wide association studies (GWAS) have identified four new genetic variants associated with migraine [4]. These variants are linked to either neurotransmitter disturbances or pain related pathways

but these variants only confer a small to moderate change in risk for migraine, which concurs with migraine being a heterogeneous disorder.

The pharmacological treatment options of acute migraine attacks include non-specific analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and specific treatment with serotonin (5-$HT_{1B/1D}$) receptor agonists (triptans) which are effective exclusively in migraine and cluster headache. Triptans act by reducing nociceptive neuronal activity in the TCC and other key regions within the affected pain pathway. The molecular mechanism behind this effect involves, among others, the inhibition of a release of activating neurotransmitters including glutamate and CGRP. Triptans are widely used in the treatment of acute migraine but only on average 29% of patients are free of pain 2 hours after dosing, and 20% are sustained pain free (pain free at 2 hours and no headache recurrence or use of rescue medication 2-24 hours post dose).

For the preventive treatment of migraine, a number of substances have been shown to effectively reduce the number of headache days in a given month. None of the substances currently in use for the preventive treatment have been developed for this purpose. These include betablockers (mainly metoprolol, propranolol and bisoprolol), calcium antagonists (flunarizine), anticonvulsants (topiramate and valproate) and antidepressants (amitriptyline). For the preventive treatment of chronic migraine onabotulinumtoxin A has been proven effective in reducing the number of headache days per month. Nevertheless, despite an efficacy in the overall number of patients, responder rates are far from being satisfactory leaving millions of migraineurs without an adequate treatment.

Transcutaneous vagus nerve stimulation is approved for cluster headache in the US. It is administered by transcutaneous stimulation in the neck or in the ear. Anecdotal observations in few patients suggest that the stimulation may reduce migraine frequency and intensity [5, 6]. A randomized, sham-controlled clinical trial has been conducted but results were not published. Thus, migraine is a complex disorder for which the underlying causes and the pathophysiology are only partially known. There are many potential targets for pharmacologic and non-pharmacologic treatments where neuronal stimulation by electric currents has shown promise in smaller studies.

In summary, pharmacologic treatments have not yet provided a complete solution to the treatment of migraine as not all patients respond, many patients suffer from substantial side effects, many of the used substances have a potential for unwanted drug-drug interactions, treatment is often limited or not possible when certain preexisting comorbidities exist and finally, most substances are not suitable for children or pregnant women. Therefore, there is still an unmet need for safe and effective migraine treatment.

The Chordate System is a medical device system that is used to administer kinetic oscillation stimulation (KOS) in the nasal cavity, which has obtained a CE certification in May 2021. The mechanism of action is believed to be that the mechanical stimulation by modulating activity

in the sphenopalatine ganglion has a rebalancing effect on the autonomic nervous system such that acute migraine attacks can be aborted or diminished. Exploratory treatment of patients with migraine demonstrated reduction in migraine pain intensity and attack frequency.

6 Identification and description of the investigational medical device

6.1 Device description

The investigational medical device system is the Chordate System S211, which is used to stimulate human tissue inside the nasal cavities by means of kinetic oscillations at low frequencies.

It consists of a base unit (Chordate Controller 1002630), an associated catheter (Catheter 1001245), and a headband (Headband 1001152). The Chordate Controller is an active therapeutic device intended to administer energy. The system is intended to be used by healthcare professionals in a clinical environment, including doctors, nurses and assistant nurses, trained in the use of the device system.

The **Chordate Controller** is intended to create air mediated oscillations with controlled pressure and frequency for a predetermined treatment time.

It consists of a pneumatic module with a pneumatic pressure and oscillation part (including pumps, valves, tubing etc.) and a printed circuit board assembly with an electronic microcontroller part (MCU, motor drives, pressure gauge etc.), and a user control panel (touch screen).

The system is factory pre-set with parameters for treatment of migraine.

The user is asked to enter a 4-digit randomization number. The controller contains an internal programmable database, defining if a specific randomization number shall result in normal (active) treatment, or placebo treatment (no vibrations).

The balloon part of the **catheter** is inserted into the nasal cavity of the subject. When started, the catheter is inflated and transmits kinetic oscillations to the mucous membrane of the nasal cavity. To prevent cross contamination, the catheter is for single-subject treatment and discarded after treatment completion.

The **headband** is intended to fixate the catheter during treatment; however, its use is optional. To reduce the risk of contamination between subjects, disposable hair nets will be used.

Additionally, medicinal liquid paraffin and protective hair nets (CE-marked product for medical usage) will be required.

All investigators will be thoroughly trained including practical exercises how to use the Chordate System. Traceability will be ensured by lot numbers.

For more information please refer to the Investigator's Brochure (IB) and Instructions for Use (IFU).

6.2 Storage and operating information

Operating temperature:	+15°C to +30°C
Controller and headband storage and transportation temperature:	-20°C to +50°C
Catheter storage and transportation temperature:	+5°C to +40°C
Humidity (all conditions):	20% to 80% RH non-condensing
Operating altitude:	-300 m to 2500 m
Controller input mains:	100-240 V ~, 50/60 Hz, 115VA; Protective ground
Classification:	Controller and catheter: Medical Device Directive (MDD) Class IIa Headband: MDD Class I

6.3 Manufacturer

Chordate Medical AB
Norgegatan 2
164 32 Kista, Sweden
Telephone: +46 (0)8400 11586

Visiting and delivery address from 01-Apr-2018:

Chordate Medical AB

c/o Regus
Kistagången 20B
164 40 Kista, Sweden

6.4 Indication

In this clinical investigation, the Chordate System S211 is intended to be used for the treatment of adult subjects (18 to 65 years) with chronic migraine.

7 Justification for the design of the clinical investigation

7.1 Pre-clinical experiences and biocompatibility

Pre-clinical investigations in animals have not been conducted since there is no appropriate animal model for this treatment.

The subject is not in contact with the Chordate Controller and no biocompatibility evaluation is needed. The only parts in contact with the subject are the balloon part of the catheter and the consumables; medicinal liquid paraffin and the hair net positioned under the head band. For the latter, CE-marked products for medical use will be used.

The balloon in the catheter is made from protective gloves (polyvinylchloride) that are CE-marked according to the Medical Device Directive class I and apply to EN 455-1-4. The balloon is in contact with the subject's mucosal membrane in the nasal cavity for transient use. The material (polyvinylchloride) is well known and data regarding the biocompatibility are given by the manufacturer. There are no biocompatibility issues during the transient use of the catheter.

7.2 Clinical experience

The Chordate System S211 is not yet CE-marked for migraine. However, promising results with predecessor Chordate System models were reported in early clinical studies.

The Chordate System is CE-marked for rhinitis. Two double-blind controlled clinical trials including 80 subjects with non-allergic rhinitis and rhinitis medicamentosa showed efficacy on nasal obstruction, secretion, and for some subjects itching [7].

One safety and tolerability study (PS002) with the Chordate System in 12 healthy subjects showed that the treatment was safe and well tolerated.

A double-blind study (PR003) in 207 patients with non-allergic rhinitis demonstrated that the Chordate system was more efficacious than placebo in reducing the weekly mean Total Vasomotor Rhinitis Symptom Score. There were no safety concerns. One serious adverse event (SAE) i.e. stroke two weeks after treatment has been reported but was judged to be not associated with study treatment.

So far, 2 studies with the Chordate System were performed in migraine patients (PM004 and PM005). Both studies were randomized, placebo-controlled, double-blind, multicenter studies to evaluate the performance and safety of the Chordate System.

Study PM004 investigated the effect of the Chordate System on acute migraine. In total, 51 patients with acute migraine attacks of moderate to severe intensity were enrolled. No statistically significant effects of the Chordate System on acute migraine headache pain and migraine features (pain-free rate, sustained pain free rate, time to meaningful relief, migraine associated symptoms, migraine derived disabilities, or global impression) were shown. A total of 42.3% in the active group and 32.0% in the placebo group showed headache relief. Rescue medication was taken by 57.7% subjects in the active group and 64.0% in the placebo group at 24 hours after treatment. A slightly higher proportion of patients with meaningful pain relief was observed in the active group compared with the placebo group.

Study PM005 investigated the potential prophylactic effect of 2 treatments with the Chordate System at an interval of 2 weeks. A total of 78 subjects were included in the performance analysis. There was no statistically significant effect on migraine frequency (days) during the complete 3 months after treatment. However, the Chordate system showed a close to significant ($p=0.0515$) effect on migraine frequency (days) 2 months after treatment.

In both migraine studies, treatment with the Chordate System was generally well tolerated. Mild transient effects on nasal and tear secretion, paresthesia of the lip, burning sensations and slight discomfort and pain were observed.

For more information please see the IB.

7.3 Justification for the clinical investigation

Migraine is a common neurological syndrome that affects approximately 10-20% of the population. The pathophysiological mechanisms leading to migraine are still poorly understood. Despite recent progress in pharmaceutical interventions to treat and prevent migraine attacks, the efficacy of these drugs is poor. In addition, for certain patients these drugs have many side effects, resulting in a large proportion of patients discontinuing the drugs. Thus, new treatment approaches are urgently needed. A drug-free approach like the Chordate System may provide a novel effective treatment and preventive measure with fewer adverse events (AEs).

The aim of this clinical investigation is to investigate the potential prophylactic effect of Chordate System treatment on migraine headache.

A randomized double-blind study with a placebo control was deemed appropriate to control for all potential influences. The concurrent placebo control group will be drawn from the same subject population as the active group. Random treatment assignment and double blinding will be used to minimize the chance of selection bias and to ensure that the active and control groups

will be similar at the start of the study and will be treated similarly during the course of the study.

8 Risks and benefits of the investigational device and clinical investigation

8.1 Potential risks

A risk analysis for the Chordate System S211 showed that the system is free from unacceptable and undesirable risks.

Results of the risk assessment are provided within the IB. For this study, eligibility criteria have been incorporated to avoid identified potential safety issues. The risks and mitigation procedures established are summarized below.

Potential risk	Mitigation
Hypersensitivity to polyvinylchloride or medicinal liquid paraffin.	Subjects with allergies to the materials of either device will be excluded.
Risks relating to biocompatibility with the Headband (allergic reaction, cross-contamination between subjects and risk of hair becoming caught in device).	A fresh hair net will be used for each subject.
Potential for risk of overtreatment and damage to nasal mucosa.	Treatment has been confined to a maximum of 20 minutes.
Small amounts of blood have occasionally been observed on the protective glove.	Subjects with a history of nose bleeds (epistaxis) and concomitant conditions that could cause excessive bleeding have been excluded. Treatment will be halted if a subject experiences a nose bleed during treatment.
In subjects with a pronounced anterior septal deviation, the balloon may be difficult to insert and the treatment be painful on the narrow side.	Subjects with a pronounced deviation will be excluded from the study.
Possible risk of complications in subjects with an implantable stimulator.	Subjects with any active implantable devices in the head and/or neck, will be excluded.
Subjects who have received radiation to the face or previous sinus surgery may have scarring and more fragile tissues which may increase the risk of bleedings and tissue damage during treatment.	Subjects with radiation to the face or who have undergone previous sinus surgery will be excluded.
Ongoing infection or malignancy of the nasal passage may prevent a therapeutic effect and increase the risk of complications during therapy.	Subjects who have been diagnosed with nasal malignancy will be excluded from the study. Subjects with an ongoing nasal infection will be excluded from treatment.

Although there are no anticipated risks to mother or fetus, women who are pregnant or at risk of being pregnant at the time of treatment will also be excluded.

The following device-related effects were observed during treatment with the Chordate System. These effects are not serious, but could be perceived as disturbing.

The following adverse device effects (ADE) are anticipated during the insertion of the catheter in the nasal cavity:

- Slight discomfort
- Slight pain
- Mild burning sensation
- Sneezing
- Increased tear secretion

The following ADEs are considered anticipated during treatment with the Chordate System:

- Sneezing
- Increased nasal secretion
- Increased tear secretion
- Paresthesia of the lip
- Slight pain
- Slight discomfort
- Mild burning sensation
- Minor epistaxis (at withdrawal of catheter)

All these effects are short-lasting and cease within a few minutes after treatment completion. As these are anticipated effects, if symptoms are mild, these should not be reported as an AE or ADE. However, if these are moderate or severe, these must be reported as AE or ADE.

8.2 Potential benefits

Anecdotal evidence has pointed to a potentially positive effect of treatment with the Chordate System on migraine frequency.

A recent randomized, placebo-controlled, double-blind pilot study to investigate the potential prophylactic effect of 2 treatments with the Chordate System S200 at an interval of 2 weeks did not show a statistically significant effect on migraine frequency (days) during the complete 3 months after treatment; however, a close-to-significant effect on migraine frequency (days) was observed 2 months after treatment.

The anticipated benefits of treatment within this clinical investigation include:

- Reduced frequency and/or severity of migraine attacks, which in addition to improving subject's quality of life, could also potentially reduce the amount of medication(s) required and associated risks related to these.

- Potential improvement of the situation for patients who cannot currently tolerate other pharmaceutical treatments due to drug interactions or comorbidities.
- For subjects not already keeping a migraine diary, collecting diary data for the clinical investigation may help in their migraine diagnosis and ongoing care.

8.3 Risk benefit rationale

No hazards were found to present unacceptable risk levels when some risks are reduced further by proper use, handling and maintenance of the system. All users of the investigational device will be trained prior to administering treatment.

There are no residual risks of the device used in this clinical investigation that have not been controlled within the IFU.

Beyond the application of the medical device system under investigation, the protocol-mandated measures imposed to the subjects virtually are associated with no additional risks.

In conclusion, the possible benefits of the clinical investigation justify the potential risks.

9 Investigators and administrative structure of the clinical investigation

The study is planned to be conducted at 5 centers in Germany and max. 6 centers in Finland under the supervision of Prof. Dr. med. Arne May (coordinating investigator).

The sponsor (Chordate Medical AB) will be responsible for the overall administration of the clinical investigation. FGK Clinical Research GmbH (in the following referred to as sponsor's representative), a contract research organization, will be responsible for project management, site monitoring, medical monitoring, handling and reporting of SAEs, serious adverse device effects (SADE), and device deficiencies and regulatory submissions.

Addresses and telephone numbers of the main responsible persons are provided in Section 4.

The study is supported by the Swedish Governmental Agency for Innovation Systems (http://www.vinnova.se/en/).

10 Objectives of the clinical investigation

Primary objective:

- To evaluate the effect of intranasal KOS using the Chordate System S211 on monthly headache days with moderate to severe intensity.

Secondary objectives:

- To evaluate the effect of treatment with the Chordate System S211 on monthly migraine days, responder rate, use of abortive medication, health-related quality of life and disability, and patient's global impression of severity;
- To evaluate the incidence and severity of AEs and ADEs following treatment with the Chordate System S211.

11 Design of the clinical investigation

11.1 General

11.1.1 Description of the design of the clinical investigation

This is a randomized, placebo-controlled, double-blind, multicenter clinical investigation of a medical device. The study consists of a 4-week screening period, a 6-week treatment period (2 weeks run-in and a 4-week observation window to assess the treatment effect), and a 4-week follow-up period.

Subjects who provided written informed consent and are eligible for the study will be asked to complete a daily diary for 4 weeks during the screening period. In the diary the subjects will record headache and migraine days, any changes in their health, and concomitant medications they may be using. The data collected in the diary during this screening period will be used as Baseline for the performance assessments.

Subjects who completed the screening period and continue to meet the eligibility criteria after review of diary entries by the investigator will be randomized (stratified by medication overuse) in a 1:1 ratio to receive either active or placebo treatment. The subjects will receive 6 treatments with the Chordate System S211 at weekly intervals at the site (Day 0 to 35; treatment Visit [V] 1 to 6) and continue to maintain a daily diary. One week after the last treatment, an end of treatment visit will be performed on Day 42 (V7).

After completion of the 6-week study treatment period (V1 to V7), subjects will be followed-up for another 4 weeks. The final visit will be performed on Day 70, 5 weeks after the last study treatment. During the 4-week follow-up, the subjects will continue to complete a daily diary.

11.1.2 Primary and secondary endpoints

Performance endpoints

Primary performance endpoint:

- Mean change from Baseline (4-week screening period) in monthly headache days with moderate to severe intensity in 4-week performance assessment period (V3 to V7).

Secondary performance endpoints:

- Mean change from Baseline in monthly headache days with moderate to severe intensity in follow-up period;
- Mean change from Baseline in monthly migraine days;
- Mean change from Baseline in monthly headache days (mild, moderate and severe intensity) in 4-week performance assessment period (V3 to V7);
- Proportion of subjects with 30% or greater reduction in headache days of moderate to severe intensity;
- Proportion of subjects with 50% or greater reduction of headache days of moderate to severe intensity;
- Change in the use of acute (abortive) medication;
- Change in migraine-specific quality of life questionnaire (MSQ), headache impact test-6 (HIT-6), and patient global impression of severity (PGI-S).

Safety endpoint

- Frequency, severity, device-relationship, and outcome of AEs.

All performance measurements used in this study are established migraine evaluations that have been validated as reliable and relevant. The measures of safety used in this study are routine clinical procedures.

11.1.3 Subject identification

Subjects will be assigned a unique 4-digit number, with the first 2 digits identifying the site and the last 2 digits identifying the subject, e.g. 01-01. At each site the investigator will assign numbers to subjects in ascending order e.g. 01, 02, 03 etc.

11.1.4 Duration of the clinical investigation

The overall duration of the clinical investigation including enrollment and treatment of all subjects is anticipated to be 1.5 years with an expected enrollment period of about 9 months.

The duration of the clinical investigation for each participating subject is about 14 weeks.

11.2 Treatments, precautions and restrictions

11.2.1 Investigational device

Packaging and labeling

The investigational device will be labeled according to applicable guidelines and national legal requirements.

Treatment settings and protocol

The investigational device will only be used as part of the clinical investigation. Treatment with the device will be in compliance with the clinical investigation plan (CIP) and manufacturer's IFU. Devices will be supplied to the site with pre-set pressure/frequency to be used for the clinical investigation. Any deviation from the prescribed technique and timing as described in the IFU will be recorded as a deviation. A comment explaining the deviation must be given within the paper case report form (pCRF).

The investigator will enter a 4-digit randomization number. The controller contains an internal programmable database, defining if a specific randomization number shall result in normal (active) treatment or placebo treatment (no oscillations).

Treatment time will be 10 minutes in each cavity (a total of 20 minutes per treatment) at 85 Hz and 80 mbar. Subjects should be in an upright position. First, the headband will be placed on the subject's head. The catheter's balloon part will be dipped in liquid paraffin and inserted into the subject's nostril (start on any side). The headband's fixation arm and catheter will be connected such that the catheter is kept in the correct position. For a detailed description please see the IFU.

The pre-set frequency (85 Hz) and pressure (80 mbar) will be used in the treatment of all subjects. All subjects should receive the pre-set 10 minutes of continuous treatment time per nostril. Once one nostril has been treated, the investigator will treat the other nostril with a minimum of delay.

11.2.2 Precautions and restrictions

Treatment with the Chordate System may not be performed in subjects with a body temperature >38.5°C.

11.2.3 Methods of assigning subjects to device groups

Subjects will be randomly assigned in a 1:1 ratio to active or placebo treatment by means of a computer-generated randomization list. Randomization will be stratified by medication overuse (yes/no) at V1.

Medication overuse is defined as regular overuse for >3 months of one or more acute symptomatic drugs (according to the IHS classification):

- Ergotamine, triptans, opioids or combination analgesic medications on ≥10 days per month on a regular basis for >3 months;
- Simple analgesics or any combination of ergotamine, triptans, analgesics or opioids on ≥15 days per month on a regular basis for >3 months without overuse (≥10 days) of any single class alone.

The Chordate System S211 can deliver normal (active) treatment or placebo treatment. The user will enter the randomization number assigned to the patient before start of treatment, and based on a hidden randomization table; the controller will either deliver active or placebo treatment.

The controller acts in one of two modes:

- Active treatment: The controller creates air-mediated kinetic oscillations with regulated pressure and frequency during a preset treatment time.
- Placebo treatment: Placebo treatment is similar to active treatment, but with no oscillations.

It is difficult to discern any difference between active and placebo treatment.

11.2.4 Investigational medical device accountability

Shipment, receipt, and return of all clinical investigational devices will be tracked and documented by the monitor and investigator. Product name, amount, lot numbers, and expiry dates will be documented for investigational devices provided to each investigational site. The disposition of devices (used, not used, or returned) will be recorded. When the treatment period is complete or at the latest during the site close out visit, the monitor will ensure that all investigational devices are returned to the sponsor. As the treatment is administered by the investigator only, compliance will be controlled by the device accountability log. Single use products, i.e. hair nets and catheters, will be disposed at the sites according to local routine.

11.2.5 Previous and concomitant medications and treatments

Subjects must be on a stable prophylactic migraine medication regimen, if any, during the 3 months prior to screening and maintain this regimen (no change in type, frequency or dose) from screening to end of follow-up. No new prophylactic migraine medication may be initiated. Treatment with Botox is not allowed during the study (from screening to end of follow-up).

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator at any time.

Subjects can use their regular acute migraine medication, when necessary, during the course of the clinical investigation. However, all such use and any changes must be documented in the diary by the subjects.

The diary will be used to collect data about the use of concomitant medication in combination with discussions with the subject and medical record review. The site will record all concomitant medications in the appropriate sections of the pCRF.

Subjects will not be included in the investigation if they have previously been implanted with a stimulator or any implantable device in the head and/or neck or a pacemaker/ defibrillator, or if they have previously undergone sinus surgery or received treatment with therapeutic x-ray intervention in the facial region.

11.3 Subjects

11.3.1 Number of subjects

Approximately 148 subjects will be enrolled in order to achieve at least 132 subjects evaluable for the primary performance endpoint. If during the conduct of the study the drop-out rate proves to be higher than expected (>10%), enrollment will continue until at least 132 subjects were assessed for the primary endpoint.

11.3.2 Inclusion criteria

1. The subject is legally competent, has been informed of the nature, the scope and the relevance of the study, voluntarily agrees to participation and the study's provisions, and has duly signed the informed consent form (ICF);
2. Male or female aged between 18 and 65 years (inclusive) at the time of providing informed consent;
3. Diagnosed as suffering from chronic migraine with or without aura (≥15 headache days per month for more than 3 months before screening including at least 8 migraine days) according to the IHS classification (International Classification of Headache Disorders [ICHD]-III beta);
4. Migraine onset before the age of 60 years;
5. Reported history of migraine for at least 1 year before screening;
6. Reported stable prophylactic migraine medication regimen, if any, during the 3 months prior to screening;
7. Able and willing to maintain current prophylactic migraine medication regimen (no change in type, frequency or dose) from screening to end of follow-up;
8. Women of childbearing potential must be willing to use highly effective contraceptive methods (failure rate <1% per year when used consistently and correctly) during the study.

11.3.3 Exclusion criteria

To enter the trial, to receive treatment and continue in the clinical investigation subjects must not meet any of the exclusion criteria as indicated below.

1. Unable to distinguish between migraine headaches and other headache types;
2. Treatment with Botox in the head/neck area within 4 months of the screening visit, or planned Botox treatment during the study;
3. Previous or ongoing treatment with an implanted stimulator or other implanted device in the head and/or neck;

4. Known pronounced anterior septal deviation, or other known relevant abnormality in the nasal cavity, including bacterial infection and wounds;
5. History of relevant sinus surgery, transsphenoidal surgery for pituitary or other lesions or cerebrospinal fluid (CSF) rhinorrhea;
6. Fitted with a pacemaker/defibrillator;
7. Previously treated with therapeutic x-ray intervention in the facial region (that could have influenced the nasal mucosa);
8. Ongoing upper respiratory infection or malignancy in the nasal cavity;
9. History of regular nose bleeding (epistaxis), or concomitant condition or medication that could cause excessive bleeding including treatment with an anticoagulant;
10. Head injury or open wound that contraindicates use of the Chordate Headband;
11. Known allergy to polyvinylchloride, a material used in the Chordate Catheter, or medicinal liquid paraffin;
12. Concurrent condition or risk of non-compliance that, in the investigator's opinion, may affect the interpretation of performance or safety data or which otherwise contraindicates participation in a clinical investigation;
13. Pregnant and lactating women;
14. Participation in a clinical investigation within 3 months of enrolment or planned participation at any time during this clinical investigation;
15. Previous participation in this study;
16. Employees of the study site or the sponsor directly involved with the conduct of the study, or immediate family members of any such individuals.

11.3.4 Subject withdrawal

Subjects are free to discontinue participation in the clinical investigation at any time, without prejudice to further treatment. Subjects who discontinue the clinical investigation should always be asked about the reason(s) for their discontinuation and about the presence of any AEs or ADEs and, if possible, be assessed by the investigator.

Subjects may be withdrawn from investigation treatment and assessments at any time, if deemed necessary by the principal investigator or sponsor.

In case of withdrawal of consent or withdrawal of the subject from the clinical investigation, AEs will be followed up by the investigator according to Section 12.5.

Subjects who are prematurely withdrawn from the study and have received at least 1 study treatment will be asked to undergo a final examination to monitor the subject's safety and document any AEs.

Subjects may be discontinued for the following reasons:

- Subject's request;
- Ineligibility including the development of any undercurrent illness(es), infections or condition(s) before treatment that might interfere with the subject's participation in the clinical investigation;
- AE(s), which in the opinion of the investigator may jeopardize the subject's health or compromise the study objectives (a corresponding AE pCRF page must always be completed);
- Poor compliance and/or disregarding the investigator's instructions;
- Major CIP violation;
- Any problem (not covered by the other categories) deemed by the investigator and/or the sponsor to be sufficient to cause discontinuation.

Every effort should be made to follow-up all subjects in accordance with this CIP. Prior to withdrawal for loss to follow-up, the investigator will try to contact the subject on 3 separate occasions and document each attempt in the subject medical records.

In case of early withdrawal, reasons, circumstances and findings should be fully described on the End of Study page in the pCRF respecting the subject's rights.

11.3.5 Subject enrollment, number, and duration of subject's participation

Subjects who have signed the ICF will be considered enrolled. Enrolled subjects who have completed the 4-week screening phase and comply with respective eligibility criteria, will be randomized.

Randomized subjects will undergo a 6-week treatment period including 6 weekly treatments with the Chordate System S211 and a subsequent 4-week follow-up period.

Approximately 148 subjects will be randomized to achieve 132 evaluable subjects (see sample size calculation Section 13.5). A group-sequential design with one interim analysis after approximately 50 subjects have completed the 6-week treatment period will be used. It will allow the premature termination of the study due to efficacy or futility or adaption of the sample size. If during the conduct of the study the drop-out rate proves to be higher than expected (>10%), enrollment will continue until at least 132 subjects were assessed for the primary endpoint.

11.4 Procedures and assessments

11.4.1 Diary

Subjects will be instructed to complete a paper diary each day from screening up to the follow-up visit. The following information will be recorded:

- Use and changes of concomitant medication (type, dose and dosing schedule);
- AEs;
- Headache and migraine days.

11.4.2 Questionnaires

During the study subjects will be asked to complete 2 self-administered questionnaires.

11.4.2.1 Headache impact test

The HIT-6 is a 6-item questionnaire that evaluates the extent of disability a subject experiences due to headache by measuring the subject's level of pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress.

11.4.2.2 MSQ

The MSQ is a 14-item, self-administered questionnaire that assesses the impact of migraine on health-related quality of life during the past 4 weeks. It includes 3 dimensions: role function-restrictive, role function-preventive, and emotional function.

11.4.3 Patient global impression of severity

The PGI-S is a 1-item questionnaire to assess the subject's impression of disease severity. The subjects will rate the severity of their condition on a scale from 1 to 4:

- 1: normal
- 2: mild
- 3: moderate
- 4: severe

11.4.4 Physical examination

A complete physical examination will be performed at screening including the following organs/body systems: general condition; skin; ears/nose/throat; head/thyroid; cardiovascular; respiratory; gastrointestinal; lymphatic; musculoskeletal; neurological; genitourinary; endocrine; others (e.g. allergies). Abnormalities will be recorded in the source data and transferred in the pCRF.

11.4.5 Other assessments

- **Demography**: age, sex, race, height, weight, body mass index.
- **Medical and surgical history:** from subject interview and medical records covering relevant past medical history. Presence of allergies and pronounced septal deviation will be recorded separately.

  The following information will be documented separately in regard to migraine history:

  - Migraine onset;
  - Average headache days per month;
  - Average migraine days per month;
- **Concomitant medications** will be recorded in the pCRF. Variables are as follows: type of medication; route; dose; unit; regimen; start date; end date (with a yes/no question for 'ongoing'); reason taken.
- **Urine pregnancy test:** urine pregnancy tests will be performed in women of childbearing potential at the times specified in the schedule of assessments (Section 3).

11.4.6 Factors that may compromise the outcome

Specific subject characteristics have been included with the aim of reducing variables that could influence treatment outcomes and interpretation of these. The rationale for individual subject characteristics to be included in the clinical investigation is detailed below.

- Diagnosis of chronic migraine with or without aura according to IHS classification (ICHD-III Beta): this is a chronic migraine study and it is important to ensure that only subjects with the target indication are enrolled.
- Male or female: although females experience more migraines that males, it is important to study outcomes in both genders.
- Age 18 to 65 years: this clinical investigation is an adult migraine study. Age above 65 years is associated with higher comorbidity and concomitant medications, which can confound interpretation of treatment effects.
- Age of migraine onset before 60 years: late onset of migraine is very rare and often mimics other diseases. Treatment response in these subjects may be atypical and confound results.
- History of migraine for at least one year: this is required in order to diagnose migraine more accurately. The migraine does not need to be in its chronic form for the complete year; however, to meet the criteria for chronic migraine (see first bullet point), subjects must have ≥15 headache days per month (of which at least 8 days fulfill the IHS criteria for migraine) for more than 3 months before screening.

11.4.7 Appropriateness of measurements

The use of simple subject diaries to record migraine details is recommended by the IHS and necessary to gather treatment outcome data.

Migraine pain and associated symptoms impact on subjects' daily functioning and quality of life. The performance endpoints, and associated variables and measurements, are consequently subject self-reported and reflect these elements.

The HIT-6 and MSQ are well-established measures for the evaluation of headache-related disability in migraine patients. The PGI-S is a widely used instrument determining the subject's impression of disease severity.

A combination of AE review and ad hoc subject AE reporting (via the diary) should ensure an accurate representation of AEs occurring during the clinical investigation.

11.5 Schedule of the clinical investigation

The schedule of assessments is provided in Section 3.

11.5.1 Screening

After written informed consent is obtained, the following assessments will be performed and information will be recorded in the pCRF:

- Check of inclusion and exclusion criteria;
- Documentation of demographics and medical and surgical history;
- Physical examination;
- Documentation of prior and concomitant medication;
- Urine pregnancy test in women of childbearing potential;
- Completion of questionnaires (HIT-6, MSQ);
- Assessment of PGI-S.

A paper diary will be handed out to the subjects to be completed during the 28-day screening phase.

Where a subject fails to fulfill the inclusion and exclusion criteria, this will be documented and the signed consent form retained by the principal investigator. The subject will not be advanced any further into this clinical investigation and an End of Study pCRF page will be completed.

11.5.2 Treatment

Visit 1 (Day 0)

Prior to any study related assessment the investigator will do a SARS-CoV-2 test, if required by site policy. If the test result is positive the patient will be asked to take the measures, which the authorities require in this case. The patient may come back to the site and continue the study after these requirements are fulfilled and a negative test result is present.

Afterwards the investigator will discuss with the subject any changes in their health during the screening phase and any changes in their medication or any new concomitant medication they may have used. The investigator will also review the subject's paper diary entries and ensure that the diary has been completed accurately. Additionally, the following assessments will be performed:

- Completion of questionnaires (HIT-6, MSQ);
- Assessment of PGI-S.

Subjects who continue to meet all inclusion criteria and none of the exclusion criteria will be randomized to 1 of the 2 study treatments.

Randomized subjects will be treated as described in Section 11.2.1 and detailed in the IFU. Any AEs or device defects occurring during or after treatment will be documented in the pCRF.

Visits 2, 3, 4, 5, and 6 (Day 7, 14, 21, 28, and 35 [± 3 days each])

At each visit, subjects will receive study treatment as described in Section 11.2.1 and detailed in the IFU.

At Visit 3 additionally the following assessments will be performed:

- Completion of questionnaires (HIT-6, MSQ);
- Assessment of PGI-S.

The subjects will be asked about any AEs and changes in concomitant medication since the last visit and any new or changed information will be documented in the pCRF.

Visit 7 (Day 42 ± 3 days)

The following assessments will be performed:

- Documentation of AEs;
- Documentation of changes in concomitant medication;
- Completion of questionnaires (HIT-6, MSQ);
- Assessment of PGI-S.

11.5.3 Follow-up (Day 70 ± 3 days)

Five weeks after the last study treatment, subjects will be asked to return to the site. The following assessments will be performed:

- Urine pregnancy test in women of childbearing potential.
- Documentation of AEs;
- Documentation of changes in concomitant medication;
- Completion of questionnaires (HIT-6, MSQ);
- Assessment of PGI-S.

The investigator will complete the End of Study page in the pCRF.

11.5.4 Early termination

In case a subject prematurely discontinues the clinical investigation (for reasons see Section 11.3.4), the End of Study page in the pCRF will be completed.

In case of early withdrawal, reasons, circumstances and findings should be fully described on the End of Study page in the pCRF respecting the subject's rights.

11.5.5 Medical care upon termination of the clinical investigation

After the final visit subjects will not receive any further study-specific treatment. They will be treated according to the investigator's discretion.

11.6 Clinical monitoring

The monitor will be responsible for ensuring that the investigators are aware of their responsibilities and for securing investigator compliance with the CIP, the signed agreement, EN ISO 14155:2020 and any conditions of approval imposed by the reviewing ethics committee (EC), component authority (CA) and/or local institution. During the clinical investigation, the monitor will have regular contacts with the investigation site. These contacts will include visits by the monitor to confirm that the facilities remain adequate to specified standards and that the investigation team is carrying out the procedures stated in the CIP. All data must be accurately recorded in the pCRF and source data verification will be performed by the monitor, to verify clinical investigation compliance and the accuracy of recorded data. The investigator must permit the monitor to visit the site at regular intervals and the pCRFs and other records must be accessible during the visits. The planned extent of source data verification (SDV) is detailed in the monitoring plan. The monitor or other sponsor personnel will be available between visits if the investigator or other staff at the site needs information and/or advice.

Authorized representatives of the sponsor and/or regulatory agencies may visit the site to perform audits/inspections, including SDV. The investigator will permit authorized inspectors

to inspect all facilities and records relating to the clinical investigation and aid the inspector to perform the audit in a timely fashion. It is the joint responsibility of both the sponsor and the investigator to ensure that the clinical investigation has been conducted in line with all applicable regulations.

11.7 Training of staff

All study site personnel should be present at the site initiation visit, during which the sponsor and/or the contract research organization (CRO) who was trained in advance by the sponsor and acting on his behalf will provide documented training on use of the device, the pCRF and clinical investigation conduct. It is the responsibility of the investigator to train any member of the research team who was not present at the site initiation visit or joined the clinical investigation at a later date on the study procedures before undertaking any clinical investigation responsibilities.

A Study Personnel and Authorization Log will be completed to indicate which activities the investigator has authorized to be performed by each research team member. This must be updated before a new or existing team member undertakes any new responsibility.

The investigator will ensure that appropriate training relevant to the clinical investigation is given to the medical, nursing and other staff involved and that new relevant information for this clinical investigation is forwarded to the staff involved.

12 Adverse events, adverse device effects, and device deficiencies

12.1 Definitions of adverse events and adverse device effects

Adverse event

An AE is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons. For subjects this definition includes events whether or not related to the investigational medical device or comparator and those events related to the procedures involved (any procedure in this CIP). For users or other persons this definition is restricted to events related to the investigational medical device.

The definition of AE in this study does not include adverse experiences observed by the patient or in the patient before the investigational medical device application. Those adverse experiences occurring after provision of informed consent and prior to application of the investigational medical device will be recorded as part of the medical history. However, if the condition deteriorates at any time from date of administration of the investigational medical device during the study it should be recorded and reported as an AE.

The definition of an AE in this study does not include anticipated device effects of mild character (sneezing, increased nasal secretion, increased tear secretion, paresthesia of the lip,

slight pain, slight discomfort, mild burning sensation, minor epistaxis [at withdrawal of catheter]). A list of anticipated device effects is also provided in Section 8.1. However, increase in severity from mild of the anticipated device effects listed above will constitute an AE. Any hospitalization due to the above-mentioned conditions will constitute an SAE.

The definition of an AE in this study does also not include migraine-associated symptoms (nausea, photophobia, phonophobia and vomiting), clinical disability and headache if they remain within the same severity and frequency observed by the patient before the study device use. Any hospitalization due to the above-mentioned conditions will constitute a SAE.

Adverse device effect

An ADE is defined as an AE that is related to the use of the investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. In addition, this includes any event that is a result of a use error or intentional misuse.

Serious adverse event

An SAE is defined as any adverse event that led to any of the following: (a) death, (b) serious deterioration in the health of the subject, that resulted in any of the following: (i) life-threatening illness or injury, (ii) permanent impairment of a body structure or a body function, (iii) hospitalization or prolongation of patient hospitalization, (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, (v) chronic disease, (c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect

Serious adverse device effect

An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.

Unanticipated serious adverse device effect

An unanticipated SADE (USADE) is defined as an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

An anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk analysis report. There are no ASADEs for this clinical investigation.

12.2 Reporting of adverse events

12.2.1 Methods for eliciting adverse events

All subjects will be carefully monitored for the occurrence of AEs during the clinical investigation period from first treatment to the completion of follow-up. At clinical

investigation visits, the investigators will collect AE information using non-leading questions such as “have you experienced any new health problems or worsening of existing conditions?”. Events directly observed or spontaneously volunteered by subjects will also be recorded. In addition, subjects will be asked to contact the investigator if they feel unwell at any time between treatment and the end of their study participation.

12.2.2 Recording of adverse events

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single AE whenever possible. The investigator must record all AEs on the AE page of the pCRF.

All SAEs must be reported to the sponsor’s representative within 24 hours of the first awareness of the event on the paper SAE Report Form by fax (see Section 12.4).

Complete description of all AEs must also be available in the source documents.

Records in the pCRF should include the following information:

- Event term (diagnosis);
- Start date (and time, if relevant);
- End date (and time, if relevant);
- Continuing yes/no
- Severity;
- Action taken regarding the medical device;
- Action taken regarding the procedure (none, aborted or temporarily interrupted);
- Opinion on causality (to device or procedure) and if applicable details of the device the AE is related to (Chordate Controller, Chordate Catheter, Chordate Headband);
- Seriousness;
- Outcome.

Changes in the assessment of relationship to the investigational medical device or procedure should be clearly documented.

Any medication necessary for the treatment of an AE must be recorded on the Concomitant Medication page of the pCRF.

12.3 Assessment of adverse events

All AEs will be assessed in terms of seriousness (yes, no), severity, outcome, relationship to the investigational medical device, and relationship to study procedures.

Adverse event assigned causality (device-related or procedure-related)

Causality will initially be assessed by the investigator as:

- Related: There is reasonable temporal relation between the AE and the investigational medical device application, AND:

  There is no other explanation for the AE or the AE follows a known or expected response pattern to the investigational medical device application.

- Not related: There is an evident other explanation for the AE.

Adverse event severity

Severity describes the intensity of an event and will be assessed as:

- Mild: The AE does not interfere in a significant manner with the subject's normal functioning level. It may be an annoyance.
- Moderate: Events that cause sufficient discomfort to interfere with daily activity and/or require a simple dose of medication, e.g. minor analgesics or antiemetics; interferes to some extent with the subject's usual function.
- Severe: Events that incapacitate and prevent usual activity or require complex medication or hospitalization; interferes significantly with the subject's usual function.

Worsening changes in severity grade will constitute a new entry in the pCRF. It is expected that the stop date of the original AE will be the same as the start date of the new entry when there is a worsening in severity grade.

Intermittent AEs will only be recorded once, as long as the severity or seriousness does not change and 'intermittent' is added to the verbatim text of the AE term. If however, the AE changes from intermittent to continual, the original event should be closed out and reopened as a new AE.

Adverse event outcome

The outcome of an AE will be assessed as follows:

- Resolved: the subject has returned to his/her previous health status observed at Baseline with no subsequent problems.
- Resolved with sequelae: as a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralyzed).
- Ongoing: the subject has not yet recovered to his previous health status observed at Baseline and continues to be followed for the AE

- Death due to this event: the subject died due to the event. If the subject died due to other circumstances than the event, the outcome should be stated as death due to other event.
- Death due to other event: the subject died due to other event
- Lost to follow-up: if information on the outcome of an AE cannot be obtained after at least 3 attempts to contact a subject over the course of a 1-month period

12.4 Reporting of serious adverse events

All SAEs will be subject to expedited reporting to the sponsor and must be reported to the sponsor's representative within 24 hours of the first awareness of the event, regardless of the time that may have elapsed from the time the event occurred and regardless whether or not they are considered causally related to the investigational medical device. The investigator must complete the study-specific paper SAE Report Form provided by the sponsor's representative, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, then sign and date the SAE Report Form and send it including additional information **immediately, not later than 3 calendar days** by email to:

[redacted]

Email: [redacted]

or, in case sending an email is not possible, please fax to [redacted].

The initial report should contain as much information as possible, but as a minimum the following information will be entered:

- Subject identification;
- Initial or follow-up report;
- Medical device information (device identification; date of procedure);
- Description of event (diagnosis);
- Date of onset (and time of onset if on the day of treatment);
- Name of the investigator;
- Causality assessment (relationship to investigational device and relationship to clinical investigation procedure);

- Seriousness classification and criteria;
- Severity.

The investigator should also complete missing or requested information and submit follow-up reports until the SAE has resolved or, in the case of permanent impairment, until the SAE has stabilized. Any additional information requested by the sponsor or sponsor's representative must be provided by the investigator without delay.

Any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible; or any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate and any new findings in relation to any event described before will be reported to all Member States in which the clinical investigation is being conducted, as required by applicable EU [10] and national law, by the sponsor or sponsor's representative without undue delay

All SAEs for which **a causal relationship** between the SAE and the investigational medical device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct **cannot be excluded and** which indicates an imminent risk of death, serious injury, or serious illness **and** that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it will be reported by the sponsor or sponsor's representative immediately, but no later than 2 calendar days from the sponsor's or sponsor's representative's awareness of the new reportable event or of new information in relation with the already reported event to the all national CAs where the clinical investigation is conducted.

Any other SAEs for which a **causal relationship** between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct **cannot be excluded** or a new finding to it will be reported by the sponsor or sponsor's representative immediately, but no later than 7 calendar days from sponsor's or sponsor's representative's awareness of the new reportable event or of new information in relation with the already reported event to all national CAs where the clinical investigation is being conducted.

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SAE EMERGENCY CONTACT DETAILS

Medical Monitor: [redacted]

Phone: [redacted]

Email: [redacted]

12.5 Follow-up of adverse events

All subjects who have been exposed to the investigational medical device will be evaluated for AEs. All AEs will be evaluated beginning with onset, and must be followed up until the last day of the clinical investigation at the site, until recovery or normalization of changed laboratory parameters, or until the investigator determines that the subject's condition is stable, whichever occurs first. All SAEs judged to be related to the investigational medical device must be followed by the investigator until the subject has recovered, recovered with sequelae, died, or until the investigator determines that the subject's condition is stable, whichever occurs first. The investigator will take all appropriate and necessary therapeutic measures required for resolution of the AE, if applicable.

12.6 Pregnancy

Subjects who become pregnant during the study should discontinue the study immediately.

Pregnancies occurring during a subject's participation in the clinical investigation are subject to the same reporting timelines towards FGK as SAEs (i.e. within 24 hours after being made aware of the pregnancy) by use of a study-specific paper Pregnancy Report Form provided by FGK via email ([redacted]).

Whenever possible, the pregnancy should be followed up to determine the outcome by use of the study-specific paper Pregnancy Outcome Report Form provided by the sponsor's representative, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications.

Pregnancy follow-up should be recorded and include an assessment of the possible relationship to the investigational device of any pregnancy outcome.

12.7 Foreseeable adverse events and anticipated adverse device effects

For a list of foreseeable AEs and anticipated ADEs please refer to Section 8.1.

12.8 Device deficiencies

12.8.1 Definition of a device deficiency

A device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer..

12.8.2 Recording and reporting of product deficiencies

The investigator will notify the sponsor or within 24 hours from the site becoming aware of a device deficiency by completing the study-specific paper Device Deficiency Report Form provided by the sponsor's representative via email ([redacted]).

Where a device deficiency causes an AE, the AE page of the pCRF must be completed.

Any device deficiency that may have led to an SAE if

a) suitable action had not been taken,

b) intervention had not been made or

c) if circumstances had been less fortunate,

has to be reported as an SAE using the same methods and timelines outlined in Section 12.4.

12.8.3 Handling of deficient medical devices

Any medical device alleged to be deficient must not be used by the investigator and has to be returned to the manufacturer.

13 Statistical considerations

This section briefly summarizes the planned statistical analyses. The statistical analyses will be described in detail in a statistical analysis plan (SAP).

The assessments done before start of treatment will serve as baseline evaluations. Generally, a baseline measurement refers to the last non-missing assessment made before treatment start.

Continuous data are presented with the number of observations, mean value, standard deviation, minimum, Q1, median, Q3, and maximum value. Categorical data are presented as counts and percentages.

13.1 Analysis sets

The statistical analyses will be based on the following sets:

Safety analysis set (SAF)

The SAF will include all subjects who will be treated with the investigational medical device at least once, irrespective of the duration of use. Subjects will be analyzed as treated.

Full analysis set (FAS)

The FAS serves as the primary performance analysis set. Subjects will be analyzed as randomized.

The FAS will include subjects which fulfil the following criteria:

- Included in the SAF
- Having baseline and any post baseline data of any performance endpoint (primary performance endpoint or any of the secondary endpoints)

Per protocol (PP) analysis set

The PP analysis set will include all subjects in the FAS without any major protocol deviations. Subjects will be analyzed as treated.

The PP set (PPS) will include subjects who fulfil the following criteria:

- Included in the FAS.
- Do not have any other major protocol violations which will affect the assessment of efficacy. An example of a major protocol violation is a subject who terminates the study participation before the primary endpoint follow-up or violation of the inclusion/exclusion criteria.
- Have no imputation for the primary performance endpoint (i.e. completed the diary for 28 days after V3).
- Have full duration of study treatment.

13.2 Statistical analyses

The primary efficacy analysis will be based on the FAS. A sensitivity analysis of the primary endpoint will be performed using the PPS. All secondary efficacy outcomes will be analyzed using the FAS. Safety analyses will be based on the SAF.

The investigator will review the patient's diary and enter the number of days with headache and the number of days with migraine in the pCRF. This information will be available for the baseline period, the performance assessment period and the follow-up period.

In case a patient should have documented less than 28 days per period (but has a compliance of at least 80%), the number of headache days per period is derived as follows:

Number of headache days = (Number of headache days x 28) / Number of days observed

If a patient has a diary compliance of less than 80%, this period will not be used for statistical analysis of this endpoint.

For example, if a patient documented 24 days for one period only, and documented 6 days with headache, the derived number of headache days in this period is calculated to (6 x 28) / 24 = 7.Primary performance endpoint

Mean change from Baseline (4-week screening period) in monthly headache days with moderate to severe intensity in 4-week performance assessment period (V3 to V7).

The primary null hypothesis to be tested is

$$H_{0:}\ \mu_{active} = \mu_{placebo} \quad \text{vs}$$

$$H_{1:}\ \mu_{active} \neq \mu_{placebo}$$

where μ is the mean change from Baseline (4-week screening period) in monthly headache days with moderate to severe intensity in 4-week performance assessment period (V3 to V7).

If the data is normally distributed an analysis of covariance (ANCOVA) with treatment, baseline number of headache days, medication overuse as independent variables will be calculated to test above null hypothesis.

If the data is not normally distributed the van Elteren test will be used with medication overuse as strata to test above null hypothesis. In addition, the number of monthly headache days and change from Baseline will be presented by descriptive statistics.

Normality of data cannot be assumed, if at least one of the following items can be demonstrated on the residuals, as determined when applying the ANCOVA as described above:

- p-value using Shapiro-Wilk test on normality < 0.2
- Visual check of the QQ-plot shows: plotted points do not approximately lie on the diagonal line y = x

Secondary performance endpoints

All statistical tests for secondary performance endpoints are considered exploratory and no adjustment for multiplicity is made.

All secondary endpoints will be evaluated for the performance assessment period and the follow-up period.

Mean change from Baseline in monthly headache days with moderate to severe intensity in follow-up period

The mean change from Baseline in monthly headache days in follow-up period will be similarly analyzed as the primary performance endpoint for the performance assessment period. The analysis for the performance assessment period is covered by the primary analysis.

Mean change from Baseline in monthly migraine days

The mean change from Baseline in monthly migraine days will be similarly analyzed as the primary performance endpoint; however, the number of migraine days instead of number of headache days will be counted.

Mean change from Baseline in monthly headache days (mild, moderate and severe intensity) in 4-week performance assessment period (V3 to V7)

The mean change from Baseline in monthly headache days with mild to severe intensity will be similarly analyzed as the primary performance endpoint; however, the number of headache days with mild intensity will be included.

Proportion of subjects with 30% or greater reduction in headache days of moderate to severe intensity

The proportion of subjects with 30% or greater reduction from baseline period to performance assessment period will be presented descriptively using frequency tables.

Additionally, active and placebo treatment arms will be compared using a Chi-square test. In case of a low number of subjects per group, the Fisher's exact test will be used.

Proportion of subjects with 50% or greater reduction of headache days of moderate to severe intensity

The proportion of subjects with 50% or greater reduction from baseline period to performance assessment period will be presented descriptively using frequency tables.

Additionally, active and placebo treatment arms will be compared using a Chi-square test. In case of a low number of subjects per group, the Fisher's exact test will be used.

Change in the use of abortive medication

The change from Baseline in monthly use of abortive medication will be presented by descriptive statistics.

Headache impact test

The total HIT-6 score and change from Baseline will be presented by descriptive statistics. The number and percentage of patients in each category will be presented for each of the 6 items. The total HIT-6 score change from Baseline will be tested using a Wilcoxon rank sum test.

MSQ

The 3 dimensions of the MSQ will be presented by descriptive statistics for absolute values and changes from Baseline. The changes from Baseline will be tested using a Wilcoxon rank sum test for each of the 3 dimensions.

Patient global impression of severity

The score will be presented descriptively using frequency tables. The change from Baseline will be assessed with a shift table of baseline versus post-baseline assessments.

Furthermore, the change from Baseline in severity scale will be calculated and tested using a Wilcoxon rank sum test.

Safety endpoints

Safety variables will be analyzed based on the SAF. Adverse events will be coded by the Medical Dictionary for Regulatory Activities (MedDRA). Incidences of AEs will be summarized by preferred term (PT) and system organ class (SOC). Adverse events (SOC and PTs) will be summarized also by intensity, relationship to the medical device or procedure, and seriousness. The analysis will be based on treatment emergent AEs, i.e. AEs which started after first treatment. All AEs will be listed.

Demographic and Other Baseline Characteristics

Subject disposition, demographics, and other baseline data will be presented using summary statistics.

13.3 Interim analysis

One interim analysis will be conducted based on the primary efficacy variable (Mean change from Baseline in monthly headache days with moderate to severe intensity in 4-week performance assessment period) according to an adaptive 2-stage group-sequential design with possible sample size adaption after the interim analysis. The interim analysis includes also the possibility to stop for efficacy and to stop for futility (using a non-binding futility rule). For assessing futility, the following secondary efficacy endpoints will be considered:

- Mean change from Baseline in monthly migraine days in 4-week performance assessment period (V3 to V7)
- Mean change from Baseline in monthly headache days (mild, moderate and severe intensity) in 4-week performance assessment period (V3 to V7)
- Change in the use of abortive medication
- HIT-6 score

An alpha spending function of the O´Brien & Fleming type is chosen for the determination of critical values.

The interim analysis is planned when the first approximately 50 subjects completed the 6-week treatment period (Visit 7).

The interim analysis will be performed and assessed by an independent data monitoring committee (DMC). The DMC will operate in adherence to pre-defined rules as written down in the DMC Charter and will consist of a statistician and two medical experts. Only the DMC will have access to unblinded efficacy data.

Based on the analysis results of the primary efficacy variable, the DMC statistician may recommend a stop of the study due to efficacy or futility or an adaption of the sample size and submit his/her proposal to the sponsor (Chordate Medical AB) who is responsible for taking the appropriate actions. One action could be to involve the two other DMC members in the decision making. In this case the DMC statistician would provide all analysis results of the interim analysis (primary and secondary efficacy endpoints) to the other two DMC members. The DMC would provide its proposal to the sponsor (Chordate Medical AB) who is finally responsible for taking the appropriate actions.

The sample size re-estimation will use the primarily assumed number of subjects in case a lower re-estimation will result.

The DMC Charter details further aspects of the conduct and decision strategies of the interim analysis.

13.4 Blind data review meeting

A blind data review meeting (BDRM) will be conducted prior to data base lock based on clean data to verify the number of subjects allocated to the analysis sets, and to identify and classify the CIP deviation observed within the clinical investigation.

13.5 Sample size calculation

For the fixed sample size approach approximately 140 subjects should be enrolled in order to achieve at least 128 subjects evaluable for the primary performance endpoint. If during the conduct of the study the drop-out rate proves to be higher than expected (>10%), enrolment would continue until at least 128 subjects were assessed for the primary endpoint.

The fixed sample size estimation delivered 128 subjects (64 per group) to be sufficient to detect a difference in means between the treatment groups of the primary performance endpoint of 3 days (e.g. by assuming a change in monthly headache days in the placebo group of 2, and in the active group of 5) and assuming that the common standard deviation is 6 using a 2-group t-test with a 0.05 two-sided significance level and a power of 80%.

As one interim analysis with the possibility to stop for efficacy or to stop for (a non-binding) futility shall be introduced, the sample size has to be revisited. An alpha spending function of the O'Brien Fleming type is applied having 2 analysis stages (one interim stage and one final analysis stage). The interim analysis will be performed after approximately 50 subjects (approximately 40% of fixed sample size) have completed the 6-week treatment period (Visit 7) (unequal spaced analyses stages). The final analysis will be performed after N=132 subjects are assessable. With respect to a drop-out rate of 10% 148 patients have to be enrolled.

The calculation of critical values for the interim analysis was performed using SAS 9.4/ PROC SEQDESIGN. A group-sequential design using an O`Brien & Fleming alpha spending function with two stages (information fraction at stage 1 is 40%, an overall significance level alpha of 0.05 and beta of 0.2) has been considered. The table below shows boundaries to be met at the interim and final analysis for claiming efficacy or stop for (non-binding) futility at pre-specified information levels. Actual boundaries will be calculated with respect to the available information fraction levels at each stage of analysis.

Boundary Information (p-Value Scale)
Nonbinding Beta Boundary, Null Reference = 0

				Alternative		Boundary Values			
Stage	Information Level			Reference		Lower		Upper	
	Proportion	Actual	N	Lower	Upper	Alpha	Beta	Beta	Alpha
1	0.4000	0.364624	52.50584	-1.81152	1.81152	0.0003942	0.39397	0.60603	0.99961
2	1.0000	0.91156	131.2646	-2.86427	2.86427	0.02487	0.02487	0.97513	0.97513

Sample Sizes (N) Two-Sample Z Test for Mean Difference								
Stage	Fractional N				Ceiling N			
	N	N(Grp 1)	N(Grp 2)	Information	N	N(Grp 1)	N(Grp 2)	Information
1	52.51	26.25	26.25	0.3646	54	27	27	0.3750
2	131.26	65.63	65.63	0.9116	132	66	66	0.9167

14 Data handling and record keeping

14.1 Case report forms and data collection

Case report forms

The clinical investigation data will be collected via pCRF completed by the site's responsible persons and finally approved by the principal investigator. The CRF pages will consist of one original and two copies of each page using "No Carbon Required" (NCR) paper.

The site will archive one copy of the completed CRF with the investigator file. Completed CRF originals (i.e. the top page of the NCR paper) will be transferred to the data management of the sponsor's designee and one copy will be sent to the sponsor's designee project management

Data entering into the pCRF

All data must be entered in English. The pCRFs should always reflect the latest observations on the subject's participation in the trial. Therefore, the pCRFs should be completed as soon as possible during or after the subject's visit. It is the investigators' obligation to assure documentation of all relevant data in the patient's file, such as medical history, concomitant diseases, date of clinical trial enrolment, visit dates, results of examinations, administrations of medication, and AEs. The investigator must verify that all data entries in the pCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the investigator should indicate this in the pCRFs. The investigator will be required to sign and date the clinical data.

The query process

The monitor will review the pCRFs and evaluate them for completeness and consistency. Each pCRFs will be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the investigator or authorized designee. Any CRF corrections should be made in a way that does not obliterate the original entry. Investigators or designees must sign with their initials and date all corrections.

Any change or addition after separation of the NCR sets must be made using Data Clarification Forms (DCFs).

The investigator or designee has to carefully answer all queries issued on DCFs. Corrections necessary after the CRF has been collected from the site must be documented in a DCF. A copy of the DCF must be retained with the respective CRF at the site.

14.2 Subject records and source data

The data reported in the pCRF shall be derived from source documents and consistent with these. Certain data may be recorded directly in the pCRF, which will then be considered as source data. Source documents are all documents used by the investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the clinical investigation. They include laboratory notes, memoranda, material dispensing records, subject files, etc. The origin of source data in the clinical investigation will be further specified in a separate document ("Origin of Source Data").

It is the responsibility of the investigator and all responsible personnel at site to maintain source documents and to record essential information in the medical records in accordance with national regulations and requirements:

- Study code;
- Subject screening number and subject number;
- Confirmation and date that informed consent for participating in the study was obtained;
- Diagnosis;
- All visits during the clinical investigation period;
- All AEs/ADEs;
- Treatments and medications.

The investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the pCRF. The investigator must submit a completed pCRF for each subject who signed the consent form. Any supportive documentation submitted with the pCRF, such as laboratory or hospital records, should be clearly identified with the clinical investigation ID and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

14.3 Data management procedures

Details on data handling will be described in the Data Management Plan (DMP). The sponsor's designee will handle the data cleaning process, including logical check, medical checks, and query processes. Computerized validation check programs on completeness, correctness,

plausibility (such as range checks, cross-checks) will verify the data according to the Data Validation Plan (DVP). All identified discrepancies will be queried using DCFs and will be addressed to the investigator. The database will be soft locked when it is considered complete and accurate (i.e. all CRF pages entered, all data cleaning activities performed). The database will be hard locked after all the changes following the DRM have been done and the database is considered complete and accurate. All changes will be tracked (audit trail). Sponsor approval prior to database hard lock is mandatory.

14.4 Data retention

The investigator shall retain all study records during the clinical investigation and for the period required by the applicable regulatory requirements or for at least 15 years after the premature termination or completion of the clinical investigation, whichever is the longer. However, the investigator should contact the sponsor prior to destruction of any records or reports pertaining to the clinical investigation in order to ensure they no longer need to be retained.

The investigator must take measures to prevent accidental or premature destruction of these documents. Included in records to be retained are the subjects' medical records, signed CIP, signed consent forms, EC approval letters, product accountability records, correspondence concerning the clinical investigation and any other documents to identify the subjects (including the Subject Identification Log).

The medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

14.5 Report of the clinical investigation

A final report of the clinical investigation (a "Clinical Investigation Report") will be completed, even if the clinical investigation is prematurely terminated. The report will be prepared by FGK according to ISO 14155:2011.

The report will be submitted to regulatory authorities and ECs, as appropriate, within the timeframes defined per national regulation or by the EC.

15 Ethical and regulatory considerations

15.1 Good Clinical Practice

The investigator will ensure that this study is conducted in full conformity with the currently acknowledged revision of the Declaration of Helsinki. By acting in accordance with this CIP the study site fulfills the requirements of the International Standard ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice [GCP]).

15.2 Ethics Committee

Before the initiation of the clinical investigation, the final CIP, any amendments if applicable, the subject information sheet and consent form, as well as any additional documents which are required by national regulations and the EC will be submitted to the competent EC for review. A favorable opinion for the clinical investigation must be obtained from the EC before any subject is enrolled at a center.

If appropriate, any additional requirements imposed by the EC will be followed. Amendments to the study documents will be notified to, or approved by, the EC before implementation, if applicable.

15.3 Regulatory requirements

This clinical investigation will be submitted for authorization to the CA as required by national law. The clinical investigation will not be initiated until written authorization for the conduct of the clinical investigation, has been received from the CA. Amendments to the clinical investigation will also be submitted for authorization to the CA as applicable.

15.4 Insurance

Insurance coverage for damages emerging from the clinical investigation will be provided according to applicable legal requirements. In addition, the sponsor has taken out insurance coverage for the subjects' travelling from their homes/places of work to the site and back. During the informed consent procedure, the investigator must inform the subject accordingly. Insurance details will be provided to the subject within the subject information sheet.

15.5 Informed consent process

Before any clinical study-related activities are performed, the investigator (or authorized designee) must review the ICF and explain the clinical investigation to potential study subjects. The investigator must ensure that the subject is fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical investigation. Before consenting, the subject must be left with ample time to consider and ask questions. It must be emphasized that participation is voluntary and that the subject has the right to withdraw from the clinical investigation at any time without prejudice. The subjects must then sign and date the ICF prior to the conduct of any study procedures. The investigator must sign and date the ICF as well.

Subjects will be informed that there is a chance they may not receive the treatment due to either not meeting the eligibility criteria or the target number of subjects to be randomized into the clinical investigation having been met.

A copy of the subject information and ICF will be given to the subjects for their records. The rights and welfare of the study subjects will be protected by emphasizing to them that the quality

of their medical care will not be adversely affected if they decline to participate in this clinical investigation.

If amendments to the final CIP affect the subject's participation in the clinical investigation (e.g. a change in any procedure), the subject information and ICF must be updated to incorporate this modification, and subjects must agree to sign the amended form indicating that they re-consent to participate in the clinical investigation.

15.6 Subject confidentiality

The study CIP, documentation, data, and all other information generated will be held in strict confidence. No information concerning the clinical investigation or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Personal subject data will be kept confidential in compliance with the European Data Protection Directive [8] or the EU General Data Protection Regulation 2016/679 [9], as applicable, and other applicable international and national requirements.

The investigator must ensure that the pseudonymization (coding) of study subjects will be maintained and that their identities are protected from unauthorized parties. On pCRFs, compensation documentation, or any other documents submitted to the sponsor or sponsor's representative, subjects must be identified only by their identification codes; it is not allowed to use their names, addresses, telephone numbers, or similar information. The investigator will keep the original of the Subject Identification Log (including complete name and date of birth of each subject) in his/her file. The investigator must maintain these documents in strict confidence.

To allow compliance with GCP, all subjects will be asked for consent regarding the access to their personal clinical study-related data for monitoring, audits, and inspections as well as regarding transmission and storage of their pseudonymous data; a respective statement will be part of the ICF. Professionals getting access to source data for monitoring, audits and inspections are bound to preserve strict confidentiality.

16 Amendments to and deviations from the CIP

16.1 Amendments

Any change to the CIP concerning the purpose of the study, the study design or the subject's eligibility can only be made in form of a written amendment to the CIP. Such amendments have to be discussed and signed by the sponsor, the coordinating investigator, and the principal investigator(s) before implementation (see also Section 15.2).

Amendments that might have an impact on study procedures to be performed and/or the well-being of the subject require a further ICF that is to be signed by all subjects enrolled in the clinical investigation who are affected by the amendment.

The sponsor or sponsor's representative will distribute CIP amendments to the investigators.

16.2 Deviations

A CIP deviation is a failure to follow, intentionally or unintentionally, the requirements of the CIP. As required by national regulation or guidelines, requests for deviations and reports of deviations will be provided to the EC if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation.

Under emergency circumstances deviations from the CIP may proceed without prior approval by the sponsor and favorable opinion of the EC if the rights, safety and well-being of human subjects need to be protected. Such deviations will be documented and reported to the sponsor and the EC as soon as possible in accordance with national regulations.

Where the monitor or sponsor identifies that the investigator is out of compliance, this will be notified to the investigator in writing, with a request to correct the source of the deviation immediately. Corrective action will be implemented to avoid repeated non-compliance, which will usually include re-training and may include terminating the clinical investigation at the site. Depending on the nature of such deviations, they will either be recorded by the investigator on the paper deviation form or completed by the monitor via the paper deviation form and signed by the investigator.

All CIP deviations will be listed and if the subjects concerned will be evaluable for analysis will be discussed in a data review meeting prior to the statistical analysis.

The sponsor is responsible for analyzing deviations and assessing their significance. Corrective action will be implemented to avoid repeated deviations, which may include suspending the clinical investigation and/or amending the CIP.

17 Suspension or premature termination of the clinical investigation

The sponsor reserves the right to terminate or suspend the clinical investigation for any reason (e.g. safety reasons, new data on the risk/benefit assessment, ethical or administrative reasons). Written notice, outlining the reasons for the termination, will be submitted to the investigators in advance of such termination. The sponsor will provide instructions if assessments beyond the regular per protocol procedures should be necessary.

The sponsor may suspend enrollment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total subject number, or non-compliance with the CIP or other clinical research requirements.

A principal investigator, EC, or regulatory authority (if applicable) may also suspend or prematurely terminate the clinical investigation at the investigational sites for which they are responsible.

In terminating the clinical investigation, the sponsor and the investigator(s) will assure that adequate consideration is given to the protection of subjects' interests.

If the clinical investigation is prematurely terminated, the sponsor or its representative will promptly inform the CA of the termination and its reason(s); the investigator or the sponsor (or representative) will promptly inform the EC, as specified in applicable regulations.

Permission to resume the clinical investigation after a temporary halt will be obtained from the CA and EC prior to implementation. The investigators will not resume the clinical investigation until the sponsor instructs them to do so and has confirmed that the necessary approvals are in place.

In case a patient was treated with the investigational device when the clinical investigation is suspended or prematurely terminated, every effort should be made to arrange for a final examination of such patient. Further medical care will be according to standard care at that site.

18 Unblinding

The premature breaking of the blinding code should be restricted to emergency cases in which knowledge of the administered treatment is necessary, e.g. after occurrence of SADEs or in case of detected pregnancy which has existed during treatment with the medical device but had not been detected prior treatment. Whenever possible, the medical monitor or sponsor should be contacted before breaking the blinded emergency code. Should any code be broken, the respective patient will be withdrawn from further participation in the study and a written explanation must be given by the investigator; the sponsor must be notified immediately.

19 Publication policy

It is the sponsor's intention that the results of the clinical investigation will be submitted jointly for publication including at least one publication in a scientific journal. Details of the publication policy and related sponsor, trust and investigator responsibilities are included in the Clinical Investigation Agreement.

This clinical investigation will be registered on ClinicalTrials.gov before enrolment of the first subject.

20 Approval and signatures

Clinical investigational plan approval

Clinical investigational plan agreed to by sponsor:

_____

Sponsor's signatory name (print)

_____ _____

Sponsor's signatory signature Date

Clinical investigational plan agreed to by coordinating investigator:

_____

Coordinating investigator name (print)

_____ _____

Coordinating investigator signature Date

Principal investigator agreement page for the clinical investigational plan

I agree:

- To assume responsibility for the proper conduct of the clinical investigation at this site, and to conduct the study in compliance with this CIP, any future amendments, and with any other study conduct procedures provided by the sponsor or authorized representatives.
- Not to implement any deviations from or changes to the CIP (including CIP amendments) without agreement from the sponsor and prior review and favorable opinion from the Ethics Committee and approval from the Competent Authority, if applicable, except where necessary to eliminate an immediate hazard to the subject(s), or for administrative aspects of the clinical investigation (where permitted by all applicable regulatory requirements).
- That I am familiar with the appropriate use of the investigational medical device as described in this CIP and any other information provided by the sponsor including, but not limited to, the current Investigator's Brochure or equivalent document provided by the sponsor.
- To ensure that all persons assisting me with the clinical investigations are adequately informed about the investigational medical device and of their study-related duties and functions.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the study product, and more generally about his/her financial ties with the sponsor. The sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

_____

Principal investigator name (print)

_____ _____

Principal investigator signature Date

21 References

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine – current understanding and treatment. N Engl J Med 2002;346:257-70.
2. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev. 2017 Apr;97(2):553-622.
3. Silberstein SD. Sex hormones and headache. Rev Neurol (Paris). 2000;156 Suppl 4:4S30-41.
4. Schürks M. Genetics of migraine in the age of genome-wide association studies. J Headache Pain. 2012;13(1):1-9.
5. Mauskop A. Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia. 2005;25(2):82-6.
6. Hord ED, Evans MS, Mueed S, Adamolekun B, Naritoku DK. The effect of vagus nerve stimulation on migraines. J Pain. 2003;4(9):530-4.
7. Juto JE, Axelsson, M. Kinetic oscillation stimulation as treatment of non-allergic rhinitis: an RCT study. Acta Otolaryngol. 2014;134(5):506-12.
8. European Parliament. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. [Online]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML .
9. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). [Online]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32016R0679
10. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. Available from: https://eur-lex.europa.eu/eli/reg/2017/745/oj