80 White Street, 3rd Floor
New York, New York 10013
[redacted]

Protocol

Product Name/Number:	CT-132
Protocol Number:	CT-132-R-001
Study Phase:	Pivotal
Brief Title:	Randomized Study of a Digital Therapeutic (CT-132) for the Prevention of Episodic Migraine
Protocol Title:	A Randomized Double-blind, Digital-Controlled, Parallel-Group, Virtual Study to Evaluate the Effectiveness and Safety of a Digital Therapeutic (CT-132) as Adjunctive Therapy in Late Adolescents and Adults for the Prevention of Episodic Migraine
Version:	Protocol Amendment 3
Approval Date:	08 May 2024
Medical Monitor	Medical monitor contact information will be provided separately.

Approval Signatures

Protocol Number:	CT-132-R-001
Version:	Protocol Amendment 3
Issue Date:	08 May 2024

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted] 5/9/2024

[redacted]

[redacted] 5/8/2024

[redacted]

[redacted]

5/8/2024

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PROTOCOL SUMMARY

1.1. Synopsis

Product Number	CT-132
Protocol Number	CT-132-R-001
Brief Title:	Randomized Study of a Digital Therapeutic (CT-132) for the Prevention of Episodic Migraine
Protocol Title	A Randomized Double-blind, Digital-Controlled, Parallel-Group, Virtual Study to Evaluate the Effectiveness and Safety of a Digital Therapeutic (CT-132) as Adjunctive Therapy in Late Adolescents and Adults for the Prevention of Episodic Migraine
Development Phase	Pivotal
Indication	CT-132 is a prescription digital therapeutic (PDT) indicated for the preventive treatment of episodic migraine in late adolescents and adults 18 years of age or older.

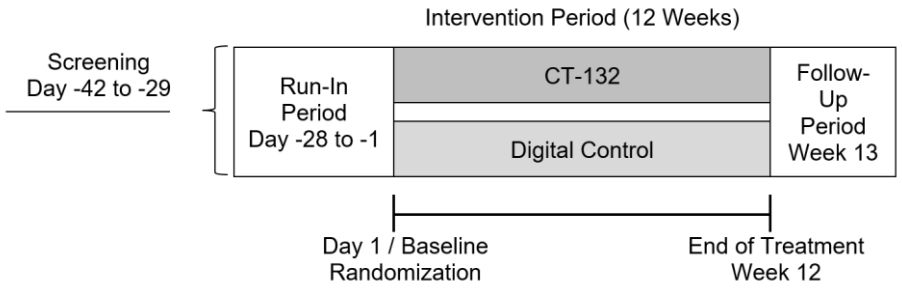
Introduction and Study Rationale	CT-132 is a novel PDT being developed by Click Therapeutics. CT-132 is a mobile application that provides an interactive, software-based intervention for the preventive treatment of episodic migraine in late adolescents and adults. The purpose of this study is to evaluate the effectiveness and safety of CT-132 relative to a Digital Control in a randomized controlled trial with an adequate sample size of participants diagnosed with episodic migraine. If demonstrated to be efficacious, CT-132 would offer an important addition to currently available treatment options.
Objective	To evaluate the effectiveness and safety of CT-132 in reducing the number of monthly migraine days (MMDs), compared with a Digital Control, among late adolescents and adults with episodic migraine.
Criteria for Evaluation	All effectiveness endpoints are evaluated as a comparison between the treatment group and the control group. A participant's baseline MMDs and MHDs will be the total number of migraine days recorded during the 28-day run-in period. The Week 12 MMDs and MHDs will be the total number of migraine days recorded over the previous 28 days (Weeks 9-12). <u>Primary Effectiveness Endpoint</u> • Change in the number of MMDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12). <u>Secondary Effectiveness Endpoints</u> • Proportion of participants who have at least a 50% reduction from baseline (28-day run-in period) in the number of MMDs to Week 12 (previous 28 days, Week 9 through Week 12). • Change from baseline (28-day run-in period) in the number of MMDs recorded over the previous 28 days at Week 4 and at Week 8. • Change from baseline (28-day run-in period) in the mean number of MMDs over 12 weeks. • Change in the number of headaches with at least moderate severity from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12). • Change from baseline (28-day run-in period) in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) total score over the previous 28 days at Week 4, Week 8, and Week 12. • Change from baseline (28-day run-in period) in the Migraine Disability Assessment (MIDAS) to Week 12 (previous 28 days, Week 9 through Week 12). • Change from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12) in the number of migraines with use of an acute medication.

	• Change in the number of MHDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12).
	
	<u>Exploratory Endpoints</u>
	
	• [redacted]
	• Monthly headache days (MHDs)
	  o Change from baseline (28-day run-in period) in the number of MHDs recorded over the previous 28 days at Week 4 and at Week 8
	  o Proportion of participants who have at least a 50% reduction from baseline (28-day run-in period) in the number of MHDs at Week 12 (previous 28 days, Weeks 9 through Week 12)
	  o Change from baseline (28-day run-in period) in the mean number of MHDs over 12 weeks.
	• Patient Global Impression of Change (PGI-C) score at Week 12
	• Shift from High Frequency Episodic Migraine (HFEM) at baseline (28-day run-in period) to Very Low Frequency Episodic Migraine (VLFEM) or Low Frequency Episodic Migraine (LFEM) at Week 12 (previous 28 days, Week 9 through Week 12)
	
	<u>Safety Endpoints</u>
	
	• Frequency and severity of AEs, serious AEs, and discontinuation from the study due to AEs
	• Frequency and severity of AEs related to the worsening of migraine

Study Design	This is a randomized double-blind, digital-controlled, parallel-group, virtual study to assess the effectiveness and safety of CT-132 in late adolescents and adults for the prevention of migraine in comparison to a Digital Control.

The study consists of an up-to-14-day screening period, a 28-day run-in period, a 12-week double-blind intervention period, and an up-to-7-day follow-up period for safety assessments.

Study Design Schema



Screening Period (Day -42 to -29)

All participants will enter a screening period of up to 14 days to determine eligibility. Eligible participants must report having had at least four migraine days per month in the three months prior to the Screening Visit (a month is defined as 28 days).

Prior to entering the screening period, participants will be asked to download the [redacted] App (separate from the Study App) in order to provide consent to the trial and complete trial assessments, including self-administered scales.

Run-In Period (Day -28 to -1)

After completing the study onboarding activities, eligible participants will be contacted to schedule a remote video call to verify their identity and their migraine medication prescriptions. Once reviewed and verified, participants will be introduced to the Study App by downloading and installing the application onto their personal iPhone or Android smartphone. Only the eDiary component of the Study App will be activated. The eDiary contains items from the Migraine Disability Index (MIDI).

Participants will then enter a 28-day run-in period during which they will enter daily headache information within the Study App to establish their baseline MMDs and determine Study App adherence and performance. Adherence to the onboarding requirements will be assessed by the investigator prior to randomization at the baseline visit.

Baseline Virtual Visit (Day 1)

	After completing the 28-day run-in period, the participant will be contacted for a Baseline Visit to review and confirm eligibility. Participants will be considered eligible for study entry based on all of the following criteria: • Continuing to meet all other inclusion and no exclusion criteria, based on investigator assessment. • Understanding of and adherence to the onboarding requirements and Study App (at 80% or greater adherence). • Reporting within the Study App between 4-14 migraine days (inclusive) during the 28-day run-in period. • Agreeing to complete the 12-week study intervention in good faith at the time of baseline virtual visit. Eligible participants will then be randomly assigned in a 1:1 ratio (CT-132: Digital Control) and the assigned full therapeutic app will be activated. Assessments and activities during this period will be performed remotely by telemedicine technology visits according to the SoA (Section 1.2). <u>Double-Blind Intervention Period (12 Weeks)</u> During the 12-week intervention period, the Study App will deliver either CT-132 or the Digital Control. Participants may use their prescribed medication to treat episodic migraine (including changes in medication or dosage) as needed while continuing to use the Study App on their regular schedule. Assessments and activities during this period will be performed remotely according to the Schedule of Activities and Assessments (Section 1.2). <u>Follow-Up Period (Up to 1 week)</u> Within one week of completion of the 12-week intervention period or withdrawal from the study, participants will complete the follow-up activities according to the Schedule of Activities and Assessments (Section 1.2).
Planned Number of Participants	Approximately 558 participants will be randomized in this study.
Study Centers	This will be a fully virtual study. Participants living in the United States will be enrolled and followed remotely through telemedicine visits.
Study Entry Criteria	<u>Inclusion Criteria</u> A participant will be eligible for entry into the study if all of the following criteria are met: 1. Willing and able to provide written informed consent to participate in the study, attend study visits, and comply with study-related requirements and assessments. 2. Lives in the United States. 3. Adult or late adolescent, 18 years of age or older at the time of informed consent.

	4. Fluent in written and spoken English, confirmed by ability to read and understand the informed consent form. 5. The following will be physician-reviewed: Participant has at least a 1-year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition. i. Age of onset of migraines prior to 50 years of age ii. Migraine attacks, on average, lasting 4-72 hours if untreated iii. Per participant report, 4 or more migraine days per month within the last 3 months prior to the Screening Visit (a month is defined as 28 days) iv. Four to fourteen migraine days during the run-in period 6. Is currently managing migraines with ≥1 prescription acute treatment and/or prescription first or second-line preventive medications, as assessed by a physician. 7. Is the sole user of an iPhone with an iPhone operating system (iOS) 14 or later or a smartphone with an Android operating system (OS) 11 or later and is willing to download and use the Study App required by the protocol. 8. Is willing and able to receive SMS text messages and push messages on their smartphone. 9. Is the owner of, and has regular access to, an email address. 10. Has regular access to the Internet via cellular data plan and/or wifi. <u>Exclusion Criteria</u> A participant will not be eligible for study entry if any of the physician-reviewed criteria are met: 1. History of basilar migraine or hemiplegic migraine. 2. Active chronic pain syndromes, such as fibromyalgia, chronic pelvic pain, or complex regional pain syndrome (CRPS). 3. Other pain syndromes (including trigeminal neuralgia), psychiatric conditions (such as major depressive episode, bipolar disorder, major depressive disorder, schizophrenia), dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments. 4. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months (48 weeks) or having met DSM-V criteria for any significant substance use disorder within the past 12 months (48 weeks) from the date of the screening visit. 5. History of use of analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen, including opioids) or butalbital on ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit or during the run-in period.

	6. Currently taking a prescription anti-calcitonin gene-related peptide (CGRP) medication for either episodic or chronic migraine. 7. Post-traumatic headache, persistent post-traumatic headache, or post-concussion syndrome. 8. Other significant episodic or chronic medical condition(s) that in the opinion of the Investigator, may confound the interpretation of findings to inform PDT development. 9. Failure to adhere with or inability to complete Study App inputs and onboarding activities during the run-in period. Participants who are not adherent during the run-in period are not eligible for study entry. 10. Previous enrollment in any digital therapeutics pilot or pivotal study for a migraine indication. 11. Participation in any other investigational clinical study while participating in this clinical study.
Test Product and Mode of Administration	Eligible participants will download and install the required Study App onto their own smartphone at the start of the run-in period. Participants will complete onboarding requirements during the run-in period and will be randomized to either CT-132 or Digital Control at the Baseline Visit (Day 1).
Study Duration	Participation in the study will last for approximately 19 weeks: • Screening Period: Up to 2 weeks • Run-In Period: 4 weeks • Intervention Period: 12 weeks • Follow-up Period: Up to 1 week
Sample Size	Approximately 558 participants are planned to be randomized in this study.
Statistical Analysis	Let μ_1 and μ_2 be the change from baseline in the MMD at the CT-132 and Digital Control arm, respectively. The null hypothesis for the primary endpoint is that the two are equal and the alternative hypothesis is that they are different. An Analysis of Covariance (ANCOVA) model will be used to test this hypothesis, where the dependent variable is the change from baseline to Week 12 in MMD for each participant. A participant's baseline MMD will be the total number of migraine days recorded during the 28-day run-in period. The Week 12 MMD will be the total number of migraine days recorded over the previous 28 days (Weeks 9-12). The model will adjust for the following covariates: treatment arm, baseline MMD, and baseline use of concomitant medications for prevention of migraine. Analysis will be conducted on the Intent-to-Treat (ITT) analysis set. Multiple imputations under Missing At Random will be used to account for early termination or missing daily reports. Further details will be described in the SAP. No adjustment for multiplicity is planned for the secondary endpoints.

1.2. Schedule of Activities and Assessments

Study Day and Visit Window	Screening/Run-In		Intervention Period				Follow-Up
	Screening[b]	Run-In	Baseline	Week 4	Week 8	Week 12/ET	Week 13
	Days -42 to -29	Days -28 to -1	Day 1 + 5 days	Day 29 ± 3 days	Day 57 ± 3 days	Day 85 ± 3 days	Days 86[c] to 92
Study Visit Number[a]	**n/a**	**1**	**2**	**3**	**4**	**5**	**6**
Informed consent	X						
Medical History	X						
Demographics	X						
Inclusion/Exclusion Criteria	X	X	X				
ID-CM	X						
Migraine Patient Journey Questionnaire	X						
MIDAS			X	X	X	X	
MSQ			X	X	X	X	
[redacted]			X	X	X	X	
PGI-C						X	
[redacted]			X	X	X	X	
[redacted]			X	X	X	X	
[redacted]			X			X	
Study App Installation		X[d]					
Activation of Full Study App			X				
Study App Engagement		X[d]	X[e]				
Randomization			X				
Study App Adherence Check[f]		X	X				

Study Day and Visit Window	Screening/Run-In		Intervention Period				Follow-Up
	Screening[b]	Run-In	Baseline	Week 4	Week 8	Week 12/ET	Week 13
	Days -42 to -29	Days -28 to -1	Day 1 + 5 days	Day 29 ± 3 days	Day 57 ± 3 days	Day 85 ± 3 days	Days 86[c] to 92
Study Visit Number[a]	**n/a**	**1**	**2**	**3**	**4**	**5**	**6**
Study App Deactivation						X[g]	
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X

Abbreviations: [redacted] DOSE-Nonadherence measure = Domains of Subjective Extent Nonadherence measure; ET = Early Termination; ID-CM = Identify Chronic Migraine; MIDAS = Migraine Disability Assessment Scale; MSQ = Migraine-Specific Quality-of-Life Questionnaire; [redacted] PGI-C = Patient Global Impression of Change scale; [redacted]

a. All study visits are virtual and conducted via telemedicine.
b. Screening Visit may occur up to fourteen (14) days before the run-in period.
c. Follow-Up activities, to include revealing the trial hypothesis, to occur within one week of the final intervention period visit. This is at least one day after the Week 12 visit (between Day 86 and Day 92) or at least one day, but no more than seven days, after an Early Termination visit.
d. Only the eDiary component of the Study App is used by the participant to complete run-in period activities. The run-in period consists of 28 days of data. However, per Study App design, participants may enter Day 28 data until Day 30. The Baseline Visit window will begin after Day 30.
e. The full Study App is used every day by the participant during the indicated period.
f. Adherence checks occur at baseline to confirm eligibility and as needed throughout the intervention period when a participant does not perform Study App Activities for 3 calendar days per Section 6.4.
g. After completion of the intervention period (Day 84), the Study App will become inert. After Day 84, or upon study withdrawal, participants will not have continued access to the content provided by the Study App.

2. INTRODUCTION

CT-132 is a novel prescription digital therapeutic (PDT) being developed by Click Therapeutics, Inc. CT-132 is a software-as-a-medical device (SaMD) mobile application that provides an interactive, software-based intervention for the preventive treatment of episodic migraine in late adolescents and adults.

2.1. Study Rationale

[redacted]

2.2. Background

2.2.1. Migraine

[redacted]

[redacted]

2.2.2. CT-132

CT-132 is a PDT intended to reduce MMDs in individuals with migraine. [redacted]

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

No AEs are anticipated specific to CT-132, due to its software-only nature. The primary potential risk to the participant that could lead to AEs is the temporary worsening of migraine symptoms. These and other potential risks may be considered minimal, and no greater than those associated with SoC [redacted] therapies for the treatment of migraine.

Participants may experience some AEs due to their underlying condition or with the use of adjunctive treatment. The risk profile of SoC used in clinical practice is well understood and is detailed in their respective package inserts.

2.3.2. Benefit Assessment

Trial participants may receive direct benefit from the interactive, software-based intervention featuring [redacted] and messaging. [redacted]

2.3.3. Overall Benefit: Risk Conclusion

CT-132 potentially delivers therapeutic effectiveness with non-significant risk. CT-132 may reduce the number of MMDs a participant experiences.

3. OBJECTIVES AND ENDPOINTS

The study objectives are to evaluate the effectiveness and safety of CT-132 in reducing the number of MMDs, compared with a Digital Control, among late adolescents and adults with migraine.

The study endpoints to support these objectives are listed in Table 1.

A participant's baseline MMD and MHD will be the total number of migraine days recorded during the 28-day run-in period. The Week 12 MMD and MHD will be the total number of migraine days recorded over the previous 28 days (Weeks 9-12).

Table 1: Study Endpoints

Primary Effectiveness Endpoint
• Change in the number of MMDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12).
Secondary Effectiveness Endpoints
• Proportion of participants who have at least a 50% reduction from baseline (28-day run-in period) in the number of MMDs to Week 12 (previous 28 days, Week 9 through Week 12). • Change from baseline (28-day run-in period) in the number of MMDs recorded over the previous 28 days at Week 4 and at Week 8. • Change from baseline (28-day run-in period) in the mean number of MMDs over 12 weeks. • Change in the number of headaches with at least moderate severity from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12). • Change from baseline (28 day run-in period) in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) total score over the previous 28 days at Week 4, Week 8, and Week 12. • Change from baseline (28 day run-in period) in the Migraine Disability Assessment (MIDAS) to Week 12 (previous 28 days, Week 9 through Week 12). • Change from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12) in the number of migraines with use of an acute medication. • Change in the number of MHDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12).

Exploratory Endpoints

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Monthly headache days (MHD)
  - Change from baseline (28-day run-in period) in the number of MHDs recorded over the previous 28 days at Week 4 and at Week 8
  - Proportion of participants who have at least a 50% reduction from baseline (28-day run-in period) in the number of MHDs at Week 12 (previous 28 days, Week 9 through Week 12)
  - Change from baseline (28-day run-in period) in the mean number of MHDs over 12 weeks
- Patient Global Impression of Change (PGI-C) score at Week 12
- Shift from High Frequency Episodic Migraine (HFEM) at baseline (28-day run-in period) to Very Low Frequency Episodic Migraine (VLFEM) or Low Frequency Episodic Migraine (LFEM) at Week 12 (previous 28 days, Week 9 through Week 12)

Safety Endpoints

- Frequency and severity of AEs, serious AEs, and discontinuation from the study due to AEs
- Frequency and severity of AEs related to the worsening of migraine

4. STUDY DESIGN

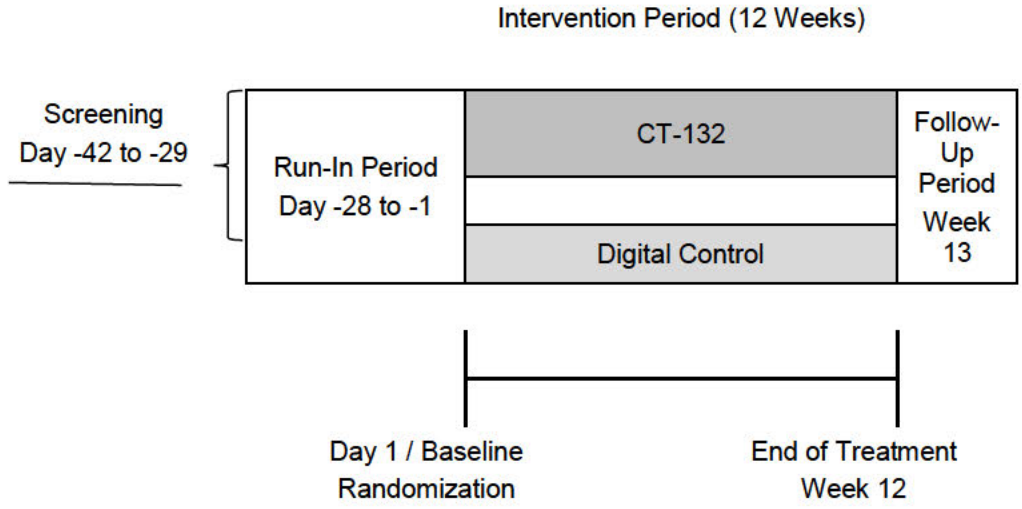
4.1. Overall Design

This is a randomized, double-blind, digital-controlled, parallel-group, virtual study to assess the effectiveness and safety of CT-132 in late adolescents and adults for the prevention of migraine in comparison to a Digital Control. Eligible participants must report having had at least four migraine days per month in the three months prior to the Screening Visit. All participants will complete an identical, pre-randomization onboarding experience, which includes verifying participant understanding of and interest in the study, and a run-in period to capture baseline MMD within the Study App.

During the run-in period and intervention period, these participants will continue to take their doctor-prescribed acute and first and second-line preventive medications for the treatment of migraine, while continuing to use the Study App.

Upon successful completion of the onboarding experience, run-in period, and confirmation of participant interest and eligibility, the participant will be randomized at the baseline study visit. The duration of participation will be approximately 19 weeks, including an up to 2-week screening period, 4-week run-in period, a 12-week double-blind intervention period, and an up to 1-week follow-up period for safety assessments.

Figure 1: Study Design Schema



To mitigate participant expectation, participants in this trial will be blinded to the effectiveness hypothesis and their treatment assignment. Eligible participants will be informed by trial staff that: a) they will participate in the trial for up to 19 weeks (including the follow-up period) and will be randomized to one of two digital therapeutic treatments and b) the purpose of the trial is to compare the effectiveness of these two digital therapeutic treatments when used in addition to SoC. Both treatment arms will be presented as possibly helping to improve migraine. No

references to CT-132 or Digital Control should be made to the participant; both should only be referred to as the Study App.

The activities and assessments during the 2-week screening period, the 4-week run-in period, the 12-week double-blind intervention period, and the 1-week follow-up period will be completed according to the Schedule of Activities and Assessments (SoA; Section 1.2). Trial staff will implement procedures remotely. Participants will be assessed based on validated standard clinician-rated and participant-rated outcome scales for migraine at screening, the intervention period, and the follow-up period. Participants will also be evaluated for safety throughout the duration of the trial.

4.1.1. Screening Period (Day -42 to Day -29)

All participants will enter a screening period of up to 14 days to determine eligibility. Eligible participants must report having had at least four migraine days per month in the three months prior to the Screening Visit (a month is defined as 28 days).

Prior to entering the screening period, participants will be asked to download the [redacted] App (separate from the Study App) in order to provide consent to the trial and complete trial assessments, including self-administered scales.

4.1.2. Run-In Period (Day -28 to Day -1)

After completing the study onboarding activities, eligible participants will be contacted to schedule a remote video call to verify their identity and their migraine medication prescriptions. Once reviewed and verified, participants will be introduced to the Study App by downloading and installing the application onto their personal iPhone or Android smartphone. Only the eDiary component of the Study App will be activated. The eDiary contains items from the Migraine Disability Index (MIDI).

Participants will then enter a 28-day run-in period during which they will enter daily headache information within the Study App to establish their baseline MMD and determine their adherence to and interest in the Study App. Adherence to the onboarding requirements will be assessed by the investigator prior to randomization at the baseline visit. Activities and assessments during this period will be performed remotely between the study personnel and the participant.

The run-in period consists of 28 days of data. However, participants may enter data at Day 28 through Day 30. The Baseline Visit window will begin after Day 30.

4.1.3. Baseline Virtual Visit (Day 1)

After completing the 28-day run-in period, eligible participants will have 3 days to complete baseline activities. Participants will attend a Baseline Visit via a telephone call to review and confirm eligibility. Participants will be considered eligible for study entry based on all of the following criteria:

- Continuing to meet all other inclusion and no exclusion criteria, based on investigator assessment.
- Understanding of and adherence to the onboarding requirements and the Study App [redacted]
- Reporting within the Study App between 4-14 migraine days (inclusive) during the 28-day run-in period.
- Agreeing to complete the 12-week study intervention in good faith at the time of baseline virtual visit.

Eligible participants will then be randomly assigned in a 1:1 ratio (CT-132:Digital Control).

The Study App downloaded during the run-in period will be utilized to deliver the full therapeutic app. Participants will continue to utilize the eDiary component in the Study App throughout the study.

The process for activating and accessing the full therapeutic application during the Baseline Visit will be the same for CT-132 digital intervention and the Digital Control. The randomization process electronically unlocks one of two experiences in the Study App: the CT-132 investigational therapy or the Digital Control. Study staff will complete the randomization process by giving the participant a code to proceed in the Study App. This code serves as a gatekeeper to confirm that the randomization process has been completed correctly and that the participant may continue in the study. This randomization process is designed in a way to minimize unblinding risk for the participant and the study staff. Participants are considered enrolled upon randomization.

4.1.4. Double-Blind Intervention Period (Day 1 - Week 12)

During the 12-week intervention period, the Study App will deliver either CT-132 or the Digital Control. The Study App will instruct participants to perform tasks daily. Participants may use their prescribed medication to treat episodic migraine, as needed, while continuing to use the Study App on their regular schedule. Assessments and activities during this period will be performed remotely according to the Schedule of Activities and Assessments. (SoA; Section 1.2)

4.1.5. Follow-Up Period (Up to 1 week)

After the end of Week 12, the Study App will become inert and no longer provide treatment. Within one week of completion of the 12-week intervention period or withdrawal from the study, participants will complete activities according to the Schedule of Activities and Assessments. (SoA; Section 1.2)

At the conclusion of a participant's participation in the study, study staff will inform the participant of the trial hypothesis (i.e., that one digital therapeutic was hypothesized to be more beneficial in preventing episodic migraine), but there was a need for a trial to confirm. Study staff will be provided with language to use for this notification.

4.2. Scientific Rationale for Study Design

The purpose of the proposed study is to evaluate the effectiveness and safety of CT-132 relative to a Digital Control in a randomized controlled trial with an adequate sample size of participants diagnosed with migraine and are taking first and second-line preventive medications. If demonstrated to be effective, CT-132 would offer an important addition to current first and second-line preventive migraine treatment options.

Recent studies on Global Burden of Diseases, Injuries, and Risk Factors have reported headache, including migraine, as a major global public health concern and one of the main causes of disability worldwide, particularly in young adults and middle-aged women. A peak in prevalence and years of life lived with disability for migraine occurs between ages 35 and 39 years. In both sexes, the percentages of all years lived with disability (YLDs) is highest in the group aged 15-49 years (migraine 8.2%) and has a high prevalence in individuals aged 50–69 years (migraine 4.2%). (GBD 2016 Headache Collaborators, 2016)

In children and early adolescents (aged under 18 years), attacks may last 2–72 hours (the evidence for untreated durations of less than two hours in children has not been substantiated). Migraine headache in children and early adolescents is more often bilateral than in adults or late adolescents; unilateral pain usually emerges in late adolescence or early adult life. (ICHD-3, 2018) Due to this similar pathophysiology and clinical symptomology in late adolescence or early adult life, the Sponsor selected a study population including late adolescents and adults aged 18 years or older. The selected patient population is similar to the population studied in pivotal trials of Erenumab and Fremanezumab indicated for the preventive treatment of migraine in adults aged 18 years or older.

Thus, as described in the device description, given the significant impact of migraine on daily activities, and the high incidence and prevalence in the population aged 18 years or older, it is clinically important that the product be evaluated and labeled for use in late adolescents and adults aged 18 years or older.

In order to reduce bias, study participants will be blinded to the hypothesis and treatment assignment, and informed that they will receive one of the two digital interventions being studied. The use of a comparator Digital Control poses minimal risk as all participants are maintained on their background therapy of SoC. See Section 6.3 for further information.

4.3. Justification for Dose

Not applicable.

4.4. End of Study Definition

The end of the study is defined as the date of the last contact, or the date of final contact attempt, for the last participant completing or withdrawing from the trial.

For the purposes of this trial, participants who complete the trial assessments at Day 84 (Week 12) will be defined as completers.

5. STUDY POPULATION

Migraine prevalence peaks in middle life and is lower in adolescents and those older than age 60 years. Migraine is also about three times more prevalent in females than males (Lipton, 2007). As guided by the FDA's Industry Guidance for *Evaluation and Reporting of Age, Race, and Ethnicity Specific Data in Medical Device Clinical Studies* (FDA's Industry Guidance, Sep 2017), study enrollment will reflect current migraine prevalence trends and will enroll participants reflecting the characteristics of clinically relevant population.

Eligible participants who are enrolled will be randomized and receive the Study App at Baseline. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

A participant will be eligible for entry into the study if all of the following inclusion criteria are met:

1. Willing and able to provide written informed consent to participate in the study, attend study visits, and comply with study-related requirements and assessments.
2. Lives in the United States.
3. Adult or late adolescent, 18 years of age or older at the time of informed consent.
4. Fluent in written and spoken English, confirmed by ability to read and understand the informed consent form.
5. The following will be physician-reviewed: Participant has at least a 1-year history of physician-diagnosed migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3):
    i. Age of onset of migraines prior to 50 years of age
    ii. Migraine attacks, on average, lasting 4-72 hours if untreated
    iii. Per participant report, 4 or more migraine days per month within the last 3 months prior to the Screening Visit (a month is defined as 28 days)
    iv. Four to fourteen migraine days during the run-in period
6. Is currently managing migraines with ≥1 prescription acute treatment and/or prescription first or second-line preventive medications, as assessed by a physician.
7. Is the sole user of an iPhone with an iPhone operating system (iOS) 14 or later or a smartphone with an Android operating system (OS) 11 or later and is willing to download and use the Study App required by the protocol.

8. Is willing and able to receive SMS text messages and push messages on their smartphone.
9. Is the owner of, and has regular access to, an email address.
10. Has regular access to the Internet via cellular data plan and/or wifi.

5.2. Exclusion Criteria

A participant will not be eligible for study entry if any of the following criteria are met:

1. History of basilar migraine or hemiplegic migraine.
2. Active chronic pain syndromes, such as fibromyalgia, chronic pelvic pain, or complex regional pain syndrome (CRPS).
3. Other pain syndromes (including trigeminal neuralgia), psychiatric conditions (such as major depressive episode, bipolar disorder, major depressive disorder, schizophrenia), dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments.
4. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months (48 weeks) or having met DSM-V criteria for any significant substance use disorder within the past 12 months (48 weeks) from the date of the screening visit.
5. History of use of analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen, including opioids) or butalbital on ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit or during the run-in period.
6. Currently taking a prescription anti-calcitonin gene-related peptide (CGRP) medication for either episodic or chronic migraine.
7. Post-traumatic headache, persistent post-traumatic headache, or post-concussion syndrome.
8. Other significant acute or chronic medical condition(s) that, in the opinion of the Investigator, may confound the interpretation of findings to inform PDT development.
9. Failure to adhere with or inability to complete Study App inputs and onboarding activities during the run-in period. Participants who are not adherent during the run-in period are not eligible for study entry.
10. Previous enrollment in any digital therapeutics pilot or pivotal study for a migraine indication.
11. Participation in any other investigational clinical study while participating in this clinical study.

5.3. Lifestyle Considerations

Participants should have routine access to their smartphones for the duration of the trial. In addition, they should be able to attend remote telemedicine visits during the trial. Participants should refrain from using alcohol, recreational drugs, or prohibited medications during the times the Study App will be accessed.

5.4. Screen Failures

A screen failure is a participant from whom informed consent is obtained and is documented in writing (i.e., participant signs an informed consent form; ICF), but who is not randomized or assigned trial intervention. Investigators must account for all participants who sign the informed consent documentation.

If a participant is found to not meet eligibility criteria for randomization into the study, the investigator will complete the required Electronic Case Report Form (eCRF) pages. The primary reason for screen fail will be recorded in the eCRF using the following categories:

- Pretreatment AE or serious adverse event (SAE) as per investigator judgement
- Did not meet eligibility criteria (inclusion and exclusion criteria)
- Lost to follow-up
- Voluntary withdrawal
- Major protocol deviation
- Study termination
- Other (specify reason)

Participant ID numbers assigned to participants who screen fail will not be reused. Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for Temporarily Delaying

Not applicable.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

The CT-132-R-001 Study App will administer participants with one of two study interventions. Study interventions are CT-132 PDT and a comparator Digital Control (Table 2).

Table 2: Study Interventions

	CT-132	**Digital Control**
Type	SaMD	SaMD
Dose Formulation	PDT under development	App
Unit Dose Strength(s)	N/A	N/A
Dosage Level(s)	N/A	N/A
Route of Administration	Digital	Digital
Use	Experimental	Comparator
IMP and NIMP	N/A	N/A
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Digital	Digital
Current/Former Name(s) or Alias(es)	N/A	N/A

PDT = prescription digital therapeutic; IMP = investigational medicinal product; N/A = not applicable; NIMP = non-investigational medicinal product; SaMD = software-as-a-medical device

6.1.1. CT-132

CT-132 is a prescription digital therapeutic intended to reduce monthly migraine days in individuals with episodic migraine. CT-132 consists of a mobile application that delivers therapeutic content and support throughout a 12-week treatment experience. CT-132 will only be accessible via prescription and is intended to be used only under the supervision of a clinician.

CT-132 is a mobile application that provides an interactive, software-based intervention for the prevention of migraine in late adolescents and adults aged 18 years or older. [redacted]

[redacted]

6.1.2. Control

A Digital Control application will be used as a comparator group in this trial. The application will be a comparable digital experience with similar daily engagement levels for the prescribed period of time.

6.1.3. Medical/Investigational Devices

1. The sponsor-manufactured medical device provided for use in this study is CT-132 and Digital Control (both referred to as the Study App) manufactured by Click Therapeutics, Inc.

2. Instructions for medical device use are provided in the CT-132-R-001 Study App Instructions.

3. All device deficiencies (including malfunction, use error and inadequate labelling) will be documented and reported by the investigator throughout the clinical investigation (see Section 10.7) and appropriately managed by the sponsor.

6.2. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

6.3. Measures to Minimize Bias: Randomization and Blinding

Study using IVRS/IWRS	All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). The IWRS will be integrated into the electronic data collection (EDC) system.

	Study team(s) will refer to the randomization information in the EDC system. The study intervention (Study App) will be downloaded, activated, and deleted at the study visits summarized in the SoA.
Blind Break (IWRS)	The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. Once a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.
Blinding	Participants will be randomly assigned in a 1:1 ratio to receive either the CT-132 or Digital Control as study intervention through the Study App. Investigators and designated personnel will remain blinded to each participant's assigned study intervention throughout the course of the study. To protect the blind between the participant and site staff, a small subset of virtual site staff will be designated as unblinded. The unblinded virtual site staff will perform regulatory and administrative duties as well as provide patient support as needed. The sponsor's trial management team will not have access to unblinded data codes and safeguards will be implemented to ensure that sponsor cannot access blinding codes during the trial.
Study Hypothesis Blind	Study participants will be blinded to the effectiveness hypothesis of the study. Both treatment arms will be presented to the participant as possible treatments for migraine. No references to CT-132 or Digital Control will be made to the participant. This approach limits the risk of participant unblinding to treatment assignment and expected effectiveness.

Assigned safety personnel may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.4. Study Intervention Adherence

[redacted]

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention after the End of the Study

Not applicable.

6.7. Treatment of Overdose

Not applicable.

6.8. Concomitant Therapy

Participants will continue to use their prescribed first and second-line preventive and acute therapies for migraine management while enrolled in this study. Participants are not allowed to use prohibited medications throughout the duration of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will complete early termination assessments as per the SoA (Section 1.2).

Events that could result in permanent discontinuation of study intervention include:

- Nonadherence
- Use of prohibited concomitant medications
- Use of prohibited recreational medications
- Investigator's discretion

The Study App on the discontinued participant's smartphone device will be disabled as described in Section 6.2.

7.2. Participant Discontinuation/Withdrawal from the Study

Study staff should make every effort to encourage participants to remain in the study and to continue to use the Study App. A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

A participant cannot withdraw consent for use of data already collected as part of the study. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Participants who prematurely discontinue study participation must complete the early termination procedures as described in the SoA (Section 1.2). Participants who discontinue use of the Study App prematurely should ideally be observed until the end of the study as if they were still using the Study App. The Study App on the discontinued participant's smartphone device will be disabled as described in Section 6.2. For all participants, the reason for discontinuation (e.g., AEs) must be recorded in the eCRF. These data will be included in the study database and reported.

Participants who are not actively using the Study App may be less motivated to adhere to the study visit schedule. Investigators and study staff should work to detect early signs of waning interest and encourage continued participation.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to attend scheduled visits and is unable to be contacted by the study investigator or designee.

The following actions must be taken if a participant fails to attend a required study visit:

- The investigator or designee must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant. Study staff will conduct a minimum of 3 communication attempts (via chat, SMS, email, or telephone). These contact attempts should be documented in the participant's record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and procedures, including their timing, are summarized in the SoA (Section 1.2). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. Every effort should be made to ensure that the protocol required assessments and procedures are completed as described. All scales should be administered by individuals who have been appropriately trained. Study procedures are described in Section 4.1. Effectiveness and safety assessments are described below.

8.1. Study Assessments

The following effectiveness assessment scales are used in this trial at the times as provided in the SoA (Section 1.2). A description of the scales and the respective scoring algorithms for all endpoints will be provided in the Statistical Analysis Plan (SAP).

8.1.1. Migraine Patient Journey Questionnaire

The Migraine Patient Journey Questionnaire is a 4-item Click-generated self-report questionnaire to characterize migraine history.

8.1.2. Monthly Migraine Days (MMD)

Participants will record the number of days per month (defined as 28 days) a participant experiences migraine events within the Study App.

8.1.3. Identify Chronic Migraine (ID-CM)

The Identify Chronic Migraine (ID-CM) (Lipton, 2016) is a 12-item self-report standardized assessment designed to assess presence of self-report migraine diagnosis and subsequently categorizes respondents as meeting diagnostic criteria for either episodic or chronic migraine.

8.1.4. Migraine-Specific Quality-of-Life (MSQ)

The Migraine-Specific Quality-of-Life Questionnaire version 2.1 (MSQ) (Rendas-Baum, 2013) is a 14-item questionnaire that measures the impact of migraine across three essential aspects of a patient's health-related quality of life over the past 4 weeks.

8.1.5. Migraine Disability Assessment Scale (MIDAS)

The Migraine Disability Assessment (MIDAS) (Stewart, 1999) questionnaire is a brief, self-report 7-item questionnaire designed to quantify headache-related disability over a 3-month period.

8.1.6. [redacted]

[redacted]

8.1.7. [redacted]

[redacted]

8.1.8. [redacted]

[redacted].

8.1.9. [redacted]

[redacted]

8.1.10. Patient Global Impression of Change (PGI-C)

The Patient Global Impression of Change (PGI-C) is a self-reported, 7-point scale depicting a patient's rating of overall improvement. PGI-C has been validated in a number of other episodic diseases against well-established measures of pain intensity, pain interference in daily life, and treatment effectiveness. (Perrot, 2019)

8.2. Study App Engagement Assessments

[redacted]

8.3. Safety Assessments

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.2.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Section 10.7.1 and Section 10.7.2, respectively.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (Section 1.2).

AEs will be divided into non-treatment-emergent AEs (non-TEAEs) and treatment-emergent AEs (TEAE). Non-TEAEs are those AEs that occurred prior to the first study treatment and TEAEs are those AEs with onset date/time at or after the first study treatment.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with other appropriate documentation (e.g., Investigator's Brochure) and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

Pregnancy will not be excluded from participating in the study. However, because pregnancy is a major life event, the sponsor will track pregnancy status. Details of all pregnancies in female participants will be collected after the start of study intervention and until the end of Week 13.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any female participant who becomes pregnant while participating in the study can continue in the study as planned. Prior to continuation of study intervention following pregnancy, the investigator must agree to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.4.6. Reporting of Investigational Device Complaints

An investigational device complaint (IDC) is any written, electronic, or oral communication by a HCP, consumer, participant, medical representative, regulatory agency, partner, or other third party that alleges Inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or use error and inadequate labeling.

For this study, all IDCs related to the Study App are reportable to the sponsor.

8.4.6.1. Eliciting and Reporting Device Complaints

During the study, possible or suspected Study App IDCs will be gathered by Click via Click's technical support resource. Instructions for reporting IDCs can be found in the Study App Instructions.

8.5. Pharmacokinetics

Not applicable.

8.6. Genetics and/or Pharmacogenomics

Not applicable.

8.7. Biomarkers

Not applicable.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary endpoint is the change from baseline in the number of MMD at Week 12. The null hypothesis for the primary endpoint is that there is no difference between the means of the treatment arms and the alternative hypothesis is that they are different.

An Analysis of Covariance (ANCOVA) model will be used to test this hypothesis, where the dependent variable is the change from baseline to Week 12 in MMD for each participant. A participant's baseline MMD will be the total number of migraine days recorded during the 28-day run-in period. The Week 12 MMD will be the total number of migraine days recorded over the previous 28 days (Weeks 9-12).

The model will adjust for the following covariates: treatment arm, baseline MMD, and baseline use of concomitant medications for prevention of migraine. Analysis will be conducted on the Intent-to-Treat (ITT) analysis set. Multiple imputations under Missing At Random will be used to account for early termination or missing daily reports. Further details will be described in the SAP.

The null hypothesis will be rejected in favor of the alternative hypothesis if the two-sided p-value is smaller than 0.05 and the result favors the CT-132 arm.

No adjustment for multiplicity is planned for the secondary endpoints.

9.2. Sample Size Determination

Assuming a difference of 1.6 in the mean MMD between the two arms, and a common Standard Deviation (SD) of 5.8, 474 participants are required for the study (237 per arm) to ensure 85% power and using a two-sided alpha of 5%.

Sample size was calculated using a two-sample t-test assuming equal variance. Assuming 15% drop out, at least 558 participants will be randomized in a 1:1 ratio to CT-132 or Digital Control.

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Analysis Set	**Description**
Consented	All participants who signed the ICF.
Enrolled	All participants who signed the ICF and completed the run-in period.
Intent-To-Treat (ITT)	The ITT set includes all enrolled participants who were randomized, based on the assigned intervention in the randomization and recorded in the database, regardless of treatment by Study App intervention. This will be the main analysis set for all effectiveness analysis.

Modified Intent-to-Treat (mITT)	[redacted]
Per Protocol (PP)	[redacted]
Safety	All randomized participants who were exposed to study intervention (completed at least one task). Participants will be analyzed according to the intervention they received. This analysis set will be used for all safety analyses.

9.4. Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1. General Considerations

For continuous variables, summary tables will provide the number of observations [n], mean, standard deviation, median, minimum and maximum. For categorical variables, summary tables will provide the number of observations [n] and frequency of each category (including missing data). Tabulations will be presented by treatment and overall, when appropriate.

Modeling and testing will be described for each endpoint.

9.4.2. Participant's Disposition

The number of participants who were screened and enrolled to the study will be presented, as well as the reason for not being randomized. The number of participants who discontinue the study will be presented by reason for discontinuation. The number of participants in the ITT, mITT, PP, and safety analysis set will be presented.

9.4.3. Demographics and Baseline Characteristics

In order to assess the comparability of the two arms at baseline, demographic and baseline characteristics data will be summarized by treatment group. These summaries will be presented for the ITT set. If there is a difference of more than five participants in the total number of participants between the ITT and the safety, mITT and PP analysis sets, the summaries will be presented for these sets.

9.4.4. Primary Endpoint

The primary analysis will include the ITT set.

The primary endpoint is change in the number of MMDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12). The primary endpoint will be analyzed using an ANCOVA model, where the dependent variable is the change from baseline to Week 12 in MMD for each participant. A participant's baseline MMD will be the total number of migraine days recorded during the 28-day run-in period. The Week 12 MMD will be the total number of migraine days recorded over the previous 28 days (Weeks 9-12).

The model will adjust for the following covariates: treatment arm, baseline MMD, and baseline use of concomitant medications for prevention of migraine. Multiple imputations under Missing At Random will be used to account for early termination or missing daily reports. Details of imputation will be described in the SAP.

Least Squares Means (LSMEANS) for the difference in the change from baseline between the two treatment arms will be presented as well as the associated 95% confidence interval and two-sided p-value to test the null hypothesis of no difference. The study will be considered successful if the two-sided p-value will be ≤ 0.05.

9.4.4.1. Sensitivity Analysis for Primary Endpoint

The primary analysis will be repeated for the mITT and PP analysis sets.

The SAP will define additional analyses to assess impact of missing data.

9.4.4.2. Subgroups

[redacted]

[redacted]

[redacted]

9.4.5. Secondary Endpoints

Analysis of secondary endpoints will include the ITT set.

- Proportion of participants that have at least 50% reduction from baseline (28-day run-in period) in the number of MMDs to Week 12 (previous 28 days, Week 9 through Week 12). The proportion of patients who have at least a 50% reduction in MMDs will be compared between the two treatment groups using the normal approximation for difference between two proportions, for each of the complete data sets. The results will be combined using Rubin's rule.
- Change from baseline (28-day run-in period) in the number of MMDs recorded over the previous 28 days at Week 4 and at Week 8 will be analyzed in the same manner as the primary endpoint.
- Change from baseline (28-day run-in period) in the mean number of MMDs over 12 weeks. The endpoint will be analyzed in the same manner as the primary endpoint.
- Change in the number of headaches with at least moderate severity from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12). An ANCOVA model will be used to analyze this endpoint.
- Change from baseline (28-day run-in period) in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) total score over the previous 28 days at Week 4, Week 8, and Week 12. An ANCOVA model will be used to analyze this endpoint.
- Change from baseline in the Migraine Disability Assessment (MIDAS) to Week 12. This endpoint will be analyzed using Wilcoxon rank-sum test.

- Change from baseline (28-day run-in) to Week 12 (previous 28 days, Week 9 through Week 12) in the number of migraines with use of an acute medication. An ANCOVA model will be used to analyze this endpoint.
- Change in the number of MHDs from baseline (28-day run-in period) to Week 12 (previous 28 days, Week 9 through Week 12). The endpoint will be analyzed in the same manner as the primary endpoint, using MHDs instead of MMDs.

The SAP will elaborate on the analysis of other endpoints, covariates and handling of missing data.

9.4.6. Multiplicity Control

No multiplicity adjustment will be made to secondary endpoints, sensitivity analyses, and subgroups.

9.4.7. Exploratory Endpoints

Exploratory endpoints will be summarized descriptively by treatment arm. Further details will be described in the SAP.

9.4.8. Safety Analysis

All safety analysis will be conducted on the safety analysis set and will be descriptive. The SAP will elaborate on the safety analysis.

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred team. The incidence of AEs and SAEs recorded through the study will be presented with the following categories:

- Number of AE and number of participants with at least one AE
- Number of SAE and number of participants with at least one SAE
- Number of related AE (based on causality as assessed by the investigator) and number of participants with at least one related AE
- Number of related SAE and number of participants with at least one related SAE
- Number of AE leading to study discontinuation
- Number of AE leading to death

9.5. Interim Analysis

No interim analysis is planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, pregnancies or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participant record, if applicable, must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent form.

The participant must be informed that his/her participant records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An independent Data Safety Monitoring Board is not planned.

10.1.6. Dissemination of Clinical Study Data

Research study results will be available on ClinicalTrials.gov and may be available through publication in peer-reviewed scientific journals.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- Guidance on completion of CRFs will be provided separately.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan (CMP).
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed by the investigator.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current participant records must be available.
- Definition of what constitutes source data can be found separately.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The first act of recruitment is the first informed consent signed and will be the study start date.

Study Termination

The sponsor or designee reserves the right to terminate the study at any time, for any reason, at the sole discretion of the sponsor.

The investigator may initiate study closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study may include but are not limited to:

- For study termination:
  - Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered to be related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the investigator as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified study personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participants will be collected during interview with the participants and by review of available records at the next visit. • Solicited AEs are predefined events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfill the definition of an AE or SAE. "Lack of effectiveness" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE, not the procedure itself.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.1. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose: (includes *any* of the following)

- **Results in death**
- **Is life-threatening**
  - The term *life-threatening* within the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for

observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether *hospitalization* occurred or was necessary, the AE will be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions, but do not constitute a substantial disruption in these.

- **Is a congenital anomaly/birth defect**

- **Other situations:**
  - Medical or scientific judgment will be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant, and/or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.2. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical or participant records to the sponsor in lieu of completion of the required form.
- There may be instances when copies of medical or participant records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical or participant records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.
  - An AE that is assessed as severe should not be confused with an SAE. *Severe* is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.
  - An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as *severe*.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.3. Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found in Electronic Trial Master File.

SAE Reporting to via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in Site Training Materials and Study Contact Information.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Not applicable.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Not applicable.

10.7. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.3 for the list of sponsor medical devices.

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any

unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.

- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:

- Led to death
- Led to serious deterioration in the health of the participant, that either resulted in:
  - A life-threatening illness or injury
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
  - A permanent impairment of a body structure or a body function
  - Inpatient or prolonged hospitalization; planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health is not considered an SAE
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
  - Chronic disease (MDR 2017/745)
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect

SADE definition

- A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

- Includes any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Recording and Follow-Up of AE and/or SAE

AE, SAE, and Device Deficiency Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the participant's records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the participant's records to the sponsor in lieu of completion of the AE/SAE form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities.
  - An AE that is assessed as severe should not be confused with an SAE. *Severe* is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

- An event is defined as serious when it meets at least one of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Device AE/SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.7.4. Reporting of SADEs

SADE Reporting

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Site Training Materials and Study Contact Information.

10.8. Appendix 8: Country-specific Requirements

Not applicable.

10.9. Appendix 9: Abbreviations and Definitions

Abbreviation	Definition
21 CFR	Code of Federal Regulations, Title 21
21 CFR 50	Code of Federal Regulations, Title 21, Part 50, Protection of Human Subjects
ADE(s)	adverse device effect(s)
AE(s)	adverse event(s)
ANCOVA	Analysis of Covariance
App	Application (software)
AST	aspartate aminotransferase
BUN	blood area nitrogen

CBT	cognitive behavioral therapy
CGRP	calcitonin gene-related peptide
[redacted]	[redacted]
CIOMS	Council for International Organizations of Medical Sciences, International Ethical Guidelines
CMP	Clinical Monitoring Plan
CRF	case report form
CRPS	complex regional pain syndrome
CT-132	A novel prescription digital therapeutic that is being developed by Click Therapeutics that delivers an interactive, software-based intervention for prevention of migraine.
DAS	Defeatist Beliefs Subscale of the Dysfunctional Attitudes Scale
DRE(s)	disease-related event(s)
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTx	digital therapeutic
eCRF	electronic case report form
EDC	electronic data collection
ET	early termination
[redacted]	[redacted]
GCP	Good Clinical Practice Guidelines
hCG	human chorionic gonadotropin
HFEM	High Frequency Episodic Migraine
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICD-10	International Classification of Diseases, Tenth Revision
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH GCP	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice Guidelines
ID-CM	Identify Chronic Migraine

IDC	investigational device complaint
IDFU	Investigational Directions for Use
IEC(s)	Independent Ethics Committee(s)
IMP	investigational medicinal product
INR	international normalized ratio
iOS	iPhone operating system
IRB(s)	Institutional Review Board(s)
ITT	intent-to-treat
LFEM	Low Frequency Episodic Migraine
MDR	medical device regulation
MedDRA	Medical Dictionary for Regulatory Activities
MHD	monthly headache day(s)
MIDAS	Migraine Disability Assessment
MIDI	Migraine Disability Index
mITT	modified intent-to-treat
MMD	monthly migraine day(s)
MMRM	Mixed Models Repeated Measures
MSQ	Migraine-Specific Quality-of-Life Questionnaire
NIMP	non-investigational medicinal product
NSAID	nonsteroidal anti-inflammatory drug
PDT	prescription digital therapeutic
PGI-C	Patient Global Impression of Change
[redacted]	[redacted]
PMR	progressive muscle relaxation
PP	per protocol
QTLs	Quality Tolerance Limits
SADE	serious adverse device effect
SAE(s)	serious adverse event(s)
SaMD	software-as-a-medical device
SAP	Statistical Analysis Plan

SDS	Sheehan Disability Scale
SMS	short message service (the most common form of text messages)
SoA	Schedule of Assessments and Activities
SoC	standard of care
TOC	table of contents
ULN	upper limit of normal
USADE/UADE	unanticipated serious adverse device effect/ unanticipated adverse device effect
VLFEM	Very Low Frequency Episodic Migraine
WHODAS 2.0	WHO Disability Assessment Schedule 2.0
YLD	years lived with disability

10.10. Appendix 10: Protocol History

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment 3	08 May 2024
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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