Otsuka Pharmaceutical Development & Commercialization, Inc.

Digital Therapeutic

CT-152

REVISED CLINICAL PROTOCOL

A Multi-center, Randomized, Controlled Trial to Evaluate the Effectiveness of a Digital Therapeutic (CT-152) as Adjunctive Therapy in Adult Subjects Diagnosed with Major Depressive Disorder

Lay Person Short Title: Trial to Evaluate the Effectiveness of a Digital Therapeutic (CT-152) as Adjunctive Therapy in Adult Subjects Diagnosed with Major Depressive Disorder

Protocol No. 345-201-00002

CONFIDENTIAL — PROPRIETARY INFORMATION

Clinical Development Phase:	Pivotal trial
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc.
Immediately Reportable Event	CCI [redacted]
Amendment 2 Approval:	03 Nov 2021

CCI [redacted]

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1 Protocol Summary

1.1 Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Investigational Digital Therapeutic: CT-152

Protocol No.: 345-201-00002

Protocol Title: A Multi-center, Randomized, Controlled Trial to Evaluate the Effectiveness of a Digital Therapeutic (CT-152) as Adjunctive Therapy in Adult Subjects Diagnosed with Major Depressive Disorder (MDD)

Protocol Lay Person Short Title: Trial to Evaluate the Effectiveness of a Digital Therapeutic (CT-152) as Adjunctive Therapy in Adult Subjects Diagnosed with MDD

Clinical Phase/Trial Type: Pivotal trial

Treatment/Indication: Major depressive disorder in adults

Objectives and Endpoints:

The objectives and endpoints are provided in table below.

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Objectives	Endpoints
Primary objective: To compare the effectiveness of CT-152 with sham, in adult subjects diagnosed with MDD who are on ADT monotherapy.	Primary efficacy endpoint: Change from baseline to Week 6 in the MADRS total score. The durability of effect will include 3 MADRS assessments at Weeks 6, 8, and 10.CCI [redacted] Key secondary efficacy endpoint: • Change from baseline to Week 6 in the GAD-7 total score. Durability based on GAD-7 will include 3 assessments, at Weeks 6, 8, and 10, demonstrating a numerically larger improvement on point estimate of the difference in the change from baseline in GAD-7 total score at Weeks 8 and 10 in CT-152 compared to sham. Other efficacy endpoints: • Change from baseline to Weeks 2 and 4 in the MADRS total score • Change from baseline to Weeks 2 and 4 in the GAD-7 total score • MADRS response rate (≥ 50% reduction from baseline) at Weeks 2, 4, and 6. • Change from baseline to Weeks 2, 4, and 6 in the CGI-S score. • Change from baseline to Week 6 in the WHODAS 2.0 total score. • Change from screening to Weeks 4 and 6 in the PHQ-9 total score. • MADRS partial response (MADRS score reduction from baseline ≥ 30% and < 50%) at Weeks 2, 4, and 6. • MADRS response rate (full or partial, defined as ≥ 30% reduction in MADRS total score from baseline) at Weeks 8 and 10.

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Objectives	Endpoints
	CCI [redacted]
Safety objective: To evaluate the safety of CT-152 in adult subjects diagnosed with MDD who are on ADT monotherapy.	Safety endpoints: • Frequency and severity of AEs, serious AEs, and discontinuations from the trial due to AEs.

Note: The sham is a control that deploys only a working memory exercise.
AE = adverse event; ADT = antidepressant therapy; CGI-S = Clinical Global Impressions-Severity; CCI [redacted]; GAD-7 = Generalized Anxiety Disorder-7; CCI [redacted] MADRS = Montgomery-Asberg Depression Rating Scale; CCI [redacted]; PHQ-9 = Patient Health Questionnaire-9; WHODAS = World Health Organization Disability Assessment Schedule.

Trial Design:

This is a multi-center, randomized, controlled trial to evaluate the effectiveness of CT-152 in adult subjects diagnosed with MDD who are on antidepressant therapy (ADT) monotherapy for the treatment of depression.

Subjects will participate in the trial for up to 13 weeks. The trial will include a screening period of up to 3 weeks, a treatment period for 6 weeks, and an extension period for 4 weeks.

Eligible subjects will be randomized to 1 of 2 digital mobile applications (CT-152 or sham) on Day 1.

To mitigate subject expectation, subjects in this trial will be blinded to the efficacy hypothesis. Eligible subjects will be informed by trial site staff that a) they will participate in the trial for up to 13 weeks and will be randomized to one of two digital therapeutic treatments and b) the purpose of the trial is to compare the effectiveness of the two digital therapeutic treatments when used in addition to ADT. Both treatment arms will be presented as possibly helping to improve MDD. No references to CT-152 or sham will be made to the subject. At the conclusion of a subject's participation in the trial, and after all final visit procedures have been completed, trial site staff will inform the subject of the trial hypothesis, ie, that one digital therapeutic was hypothesized to be more beneficial in improving depression symptoms, but there was a need for a trial to confirm.

Trial site staff will be provided with debriefing guidelines to assist in this discussion with the subject.

Trial site staff will implement procedures either by telephone or by remote visit via telemedicine technology, at all visits. The screening visit may be performed in person at the discretion of the investigator. A trial site may conduct an unscheduled visit in person or remotely at any time if needed to assess a safety issue/concern.

Remote visits will be conducted using a sponsor-designated telemedicine platform with a portal accessible by the trial site staff, and subjects will be asked to download a mobile application (separate from the investigational digital mobile application) in order to provide consent to the trial and complete trial assessments, including self-administered scales.

Prior to downloading the mobile application for conducting telemedicine visits, subjects will be asked to provide consent to participate in a registry and agree to its privacy policy and terms of service required to collect subjects' information within the telemedicine platform, including identity verification. Subjects will be required to complete the identity verification process remotely before they can electronically sign the trial consent in order to comply with 21 Code of Federal Regulations (CFR) Part 11 electronic signature requirements. Details are found in the Site Operations Manual.

The screening period begins after informed consent has been obtained. Subjects who fulfill entry criteria at the screening visit will download the digital mobile application on their smartphone and receive access to an onboarding software module. A call center can assist with the downloading of the digital mobile application. During the screening period, subjects will become familiar with the software. The subject's understanding of, and interest in, the trial will be demonstrated through adequate adherence to onboarding requirements. This will be assessed by the investigator via confirmation with the subject and completion of tasks by the subject CCI [redacted] during the allotted 3-week screening window.

Following the screening visit, subjects will be considered eligible based upon the following:

- Adherence and performance on the onboarding software module by the subject CCI [redacted]
- Continuing to meet all inclusion and no exclusion criteria based on investigator assessment.

On Day 1, the eligible subjects will be randomized 1:1 (CT-152 or sham) across approximately 50 trial sites. The sample size at any single trial site will be capped at approximately 15% of the total subjects randomized into the trial. Randomization will be stratified by trial site.

During the treatment period (Day 1 [baseline] to Week 6) subjects will have a remote visit at Weeks 2, 4, and 6 and will be contacted by telephone by the trial site at Weeks 1, 3, and 5. Subjects will be expected to be adherent with their digital mobile application exercises during the treatment period.

After Week 6, subjects will continue participation in the trial during the extension period (Weeks 7 to 10). In the extension period, the digital mobile applications will remain installed for each group. Subjects will receive brief short message service (SMS) messages reminding subjects of the previously completed CT-152 or sham treatment courses (see the "Trial Treatment" section below for further details), and will continue their ADT. Subjects will have a remote visit at Weeks 8 and 10 and will be contacted by telephone by the trial site at Weeks 7 and 9.

The end of the trial will be Week 10.

During the treatment and extension periods, a blinded and independent expert clinical rater from a centralized vendor, who will otherwise not interact with the subject, will rate and record the Montgomery-Asberg Depression Rating Scale (MADRS) remotely by telephone while remaining blinded to treatment assignment and other clinical information. This may occur separately from the remote trial site visit but must be performed within the window described in the schedule of assessments.

The Clinical Global Impressions-Severity (CGI-S) scale will be completed by designated trial site staff at remote visits that occur during the treatment period. Other assessments to be performed during the trial include the Generalized Anxiety Disorder-7 (GAD-7), World Health Organization Disability Assessment Schedule (WHODAS) 2.0, Patient Health Questionnaire-9 (PHQ-9), CCI [redacted]

During the trial, the trial site staff will also administer the Columbia-Suicide Severity Rating Scale (C-SSRS), review subject adherence to the treatment sessions during the treatment period, confirm subject adherence to their current ADT, and assess adverse events (AEs) and concomitant medications.

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Trial Population:

The trial will enroll male or female subjects aged 22 to 64 years old at the time of informed consent, with a current primary diagnosis of MDD based on the criteria in the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (*DSM-5*), single or recurrent episode, without psychotic features and do not meet criteria for MDD with mixed features subtype, and who are on ADT monotherapy. If other allowable psychiatric diagnoses are present, they must not be considered primary (causing a higher degree of distress or impairment than MDD).

Key Inclusion/Exclusion Criteria:

In addition to the criteria mentioned under Trial Population above, key inclusion criteria are as follows:

- Subjects must be in a current major depressive episode, as defined by *DSM-5* criteria and confirmed by both the Mini International Neuropsychiatric Interview (M.I.N.I) and an adequate clinical psychiatric evaluation.
- A score of Hamilton Rating Scale for Depression, 17-item ($HAM\text{-}D_{17}$) ≥ 18 at screening and the baseline visit (Day 1).
- Subject must have a reported history for the current episode of inadequate response to their current monotherapy ADT. Treatment with the current ADT must be of adequate dose and duration, defined as at least 6 weeks at a minimum therapeutic dose (or higher) according to the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) performed at screening. Inadequate response is defined as < 50% reduction in depression symptom severity per the MGH-ATRQ. Additionally, the subject must be on a stable dose of their current monotherapy ADT for a minimum of 4 weeks prior to baseline (Day 1).
- Subjects who are willing to maintain ADT treatment at current dose for the duration of their participation in the trial.
- Subjects who are the only users of an iPhone with iPhone operating system (iOS) 13.0 or greater capabilities, or a smartphone with an Android operating system (OS) 9.0 or greater capabilities, and agree to download and use the digital mobile application as required by the protocol.
- Subjects who, in the opinion of the investigator, will not require additional pharmacological intervention during the trial for the treatment of depression.
- Subjects who have successfully completed the onboarding software module in the digital mobile application during the screening period.
- Subjects who continue to consent to participate in the trial and are judged to understand the use of the digital mobile application at the baseline visit (Day 1).

Key exclusion criteria are as follows:

- Subjects with a reported inadequate response to > 1 adequate trial of ADT for the current episode. An adequate trial is defined as at least 6 weeks at a minimum therapeutic dose (or higher) according to the MGH-ATRQ. Inadequate response is defined as < 50% reduction in depression symptom severity per the MGH-ATRQ.
- Subjects who have been treated with psychopharmacological augmentation for depression in the past or in the current episode (eg, lithium, triiodothyronine, or antipsychotics added to ADT, multiple ADTs). If, in the clinical opinion of the investigator, the subject did not receive an adequate trial of an agent used for augmentation, these subjects may be considered for inclusion following discussion and approval by the medical monitor.
- Subjects who are currently receiving or have received psychotherapy within 90 days prior to screening.
- Subjects who have failed to respond to an adequate course (≥ 8 weeks) of cognitive behavioral therapy at any time in the past.
- Suicidality assessment:
  - Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) within the last 12 months prior to screening or at the baseline visit (Day 1), OR
  - Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) within the last 12 months prior to screening or at the baseline visit (Day 1), OR
  - Subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or suicidal behavior) within the last 24 months prior to screening or at the baseline visit (Day 1), OR
  - Subjects who, in the opinion of the investigator, present a serious risk of suicide.
- Subjects who at any time in the past have been treated with electroconvulsive therapy or neuro-modulation devices (transcranial magnetic stimulation, vagus nerve stimulation, or transcranial direct current stimulation, etc) for depression.
- Subjects who at any time in the past have received ketamine, esketamine, or arketamine for treatment of depression.
- Subjects who are currently using a computer, web, or smartphone software-based application or equivalent for mental health or depression. Subjects who agree to discontinue use at screening will be permitted to enter the trial.
- Subjects who have a current diagnosis of substance or alcohol use disorder (excluding nicotine) per *DSM-5* within 6 months prior to the screening visit.
- Subjects in a current major depressive episode lasting longer than 2 years.
- Subjects who are considered resistant/refractory to treatment by history and per investigator judgment.

- A lifetime diagnosis of schizophrenia, schizoaffective disorder, other psychotic disorder, or Bipolar I/II disorder, or current posttraumatic stress disorder, panic disorder, or obsessive-compulsive disorder, as assessed by the M.I.N.I.
- Current generalized anxiety disorder or social anxiety disorder as assessed by the M.I.N.I and considered to be primary (causing a higher degree of distress or impairment than MDD).
- Subjects diagnosed with any *DSM-5* personality disorder as assessed by the investigator during the psychiatric evaluation and/or from medical records.
- Depression due to a general medical condition or a neurologic disorder.
- History of seizure disorder other than a single childhood febrile seizure that fully resolved.
- Subjects who would be likely to require prohibited concomitant therapy during the trial.

Trial Site(s): This trial will be conducted at approximately 50 trial sites in the United States.

Trial Treatment, Treatment Duration, Mode of Administration:

Subjects that meet all the initial inclusion criteria and none of the exclusion criteria at screening will download and install the digital mobile application onto their own smartphone device that they will use for the trial. A dedicated call center can assist with the initial downloading of and access to the digital mobile application. The investigator will confirm the subject's understanding of, and interest in, the trial through adequate adherence to run-in onboarding requirements in the onboarding software module within a span of 7 consecutive days during the 3-week screening period (Day −21 to Day −1).

The onboarding software module will provide example cognitive control task sessions. The content of these example sessions will not include therapeutic content, so as to minimize bias once subjects are randomized to 1 of the 2 arms (CT-152 or sham).

At the baseline visit (Day 1), successful use of the onboarding software module will be confirmed. CT-152 or sham will be activated within the digital mobile application during the baseline visit with an access code.

CT-152 delivers an interactive, software-based intervention featuring cognitive-emotional training, psychotherapy lessons, psychotherapy messages, and engagement messages. Each treatment session will consist of an Emotional Faces Memory Task (EFMT) exercise and a psychotherapy lesson. Sham will serve as a control.

Sham will provide a cognitive training exercise designed to retain user interest while minimizing any therapeutic effect. Each treatment session will consist of a Shapes

Memory Task (SMT) exercise. It will present users with an analogous structure, matched for time and attention to the cognitive-emotional training exercise found in CT-152. In order to retain the intended placebo nature of the sham, it will not include EFMT or psychotherapy content.

Subjects will participate in the trial for up to 13 weeks. This includes a screening period of up to 3 weeks; due to the onboarding adherence requirement, a minimum of 7 consecutive days will be required for screening. Extensions to the screening period, if requested by the investigator, may be granted after discussion and approval by the medical monitor.

The intervention will begin the same day as the baseline visit, once the baseline visit has been completed. The subjects will progress through a treatment schedule of 18 sessions (approximately 30 - 45 minutes) at a rate of 3 sessions per week over the 6-week treatment period (Day 1 [baseline] to Week 6).

After Week 6, subjects will continue participation in the trial during the extension period (Weeks 7 to 10). In the extension period, the digital mobile applications will remain installed for each group with EFMT and SMT no longer available. Psychotherapy content provided previously will remain available for optional reference in the CT-152 group but no new therapeutic content will be introduced and no required treatment schedule is in place. The 2 groups will each receive brief SMS messages in the extension period reminding subjects of the previously completed CT-152 and sham treatment courses.

A dedicated call center is available to support the subject and the trial site on the initial downloading of and access to the digital mobile application, as well as any technical issues with the digital mobile application throughout the trial.

Subjects must be instructed by the investigator to contact the call center with any technical questions about the digital mobile application. All calls to the call center will be documented and processed. Basic user technical issues will be resolved by the call center.

If a subject contacts the call center with an AE, the call center will log the call and will immediately provide this information to the trial site and sponsor or sponsor’s designee for follow-up.

If a subject contacts the call center with a possible or suspected product quality complaint (PQC), the call center will log the call. All call records (tickets) captured by the call center will be provided to the Click Therapeutics Quality Team for PQC analysis, tracking, and resolution.

If a subject reports a possible or suspected PQC to the investigator or designee during a remote visit or telephone contact, the investigator or designee is to immediately contact the call center, which will log the call and immediately provide the information to the Click Therapeutics Quality Team.

In addition to call tracking, calls with the call center may be recorded for quality purposes. Call center contact information and processes are detailed in the Site Operations Manual.

Trial Assessments:

Assessments for Efficacy: MADRS, GAD-7, CGI-S, WHODAS 2.0, and PHQ-9.

Assessments for Safety: AEs (including AEs related to the worsening of depressive symptoms) and C-SSRS.

Screening/Other: CCI M.I.N.I, HAM-D_{17}, Antidepressant Treatment Response Questionnaire, *DSM-5* diagnosis of MDD, urine drugs-of-abuse screen, pregnancy test, and adherence check.

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will be chartered for this trial. The DMC will include at least 3 members, one of whom will be an expert in biostatistics for clinical trials, and at least one of which will have expertise in MDD treatment trials. The DMC will be convened at intervals described in the DMC charter to review data on recruitment, retention, interim analysis, and safety (including evaluation of discontinuation criteria), and to review data for completeness and quality during the trial. Discontinuation criteria will be prespecified and included in the DMC charter.

Statistical Methods:

The initial sample size is calculated to detect a 3-unit difference between CT-152+ADT and sham+ADT in the change from baseline in MADRS total score with 85% power at a 2-sided $\alpha = 0.05$ level, assuming a common standard deviation of 9. The resulting sample size is 324 evaluable subjects in total (162 subjects in each arm). To compensate for subjects that fail to have evaluable assessments of MADRS total score in the full analysis set (FAS) sample (estimated at up to 10% of all subjects), a total of 360 subjects (180 subjects in each arm) will be randomized in this trial.

Due to the limitations of applying assumptions on the treatment effect size, and in order to ensure adequate power of the trial, an unblinded interim analysis will be conducted by

a DMC. The final sample size could be increased to 540 subjects (270 subjects in each arm) as per recommendation of the DMC. Using the O'Brien-Fleming spending function, a significance level of 0.003 (2-sided) is allocated to this interim analysis. The corresponding final significance level is 0.049 (2-sided).

The null hypothesis of the statistical test comparing CT-152+ADT and sham+ADT, based on the primary efficacy endpoint, is that the change in MADRS using CT-152+ADT is equal to the change in MADRS using the sham+ADT.

The primary analysis will be conducted on the change from baseline in MADRS total score to the final on-therapy evaluation (Week 6) based on the FAS sample adjusted for the baseline MADRS total score.

CCI [redacted]. In this trial, we plan to detect a 3-point difference on the primary efficacy endpoint between the treatment groups. CCI [redacted] This trial is considered positive if the trial will be stopped at the interim analysis for efficacy, or if the p-value of the statistical comparison based on the primary efficacy endpoint at final is < 0.049.

The primary analysis will utilize mixed model repeated measurements (MMRM) with treatment, visit, treatment by visit interaction, and site as fixed effects to assess heterogeneity of treatment effects. The key secondary efficacy endpoint and other efficacy endpoints will be analyzed based on the FAS as described for the primary analysis.

The null hypothesis of the statistical test comparing CT-152+ADT and sham+ADT, based on the key secondary efficacy endpoint, is that the change from baseline to Week 6 in the GAD-7 total score using CT-152+ADT is equal to the change from baseline to Week 6 in the GAD-7 total score using sham+ADT.

The key secondary efficacy endpoint will be analyzed using the same method (MMRM) as in the primary analysis with a replacement of the interaction term of visit by baseline GAD-7 total score as a covariate.

The durability of effect of CT-152 will be assessed based on MADRS total score and GAD-7 total score at Weeks 6, 8 and 10. Change from baseline to Week 8 and 10 in the above assessments will be analyzed using MMRM as described for the primary analysis.

An unblinded interim analysis of efficacy data will be conducted on approximately the first 180 randomized subjects. The unblinded interim analysis will be carried out when these subjects have either completed the Week 6 visit or discontinued prior to Week 6.

The difference between CT-152 and sham based on the primary efficacy endpoint will be tested at the unblinded interim analysis. The sample size will be re-estimated only based on the conditional power determined at the interim analysis. The adaptive designs methodology published by Chen, DeMets, and Lan will be used to increase the sample size based on an interim estimate of the treatment effect size, possibly combined with other external information, without inflating the type I error.

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1.2 Schema

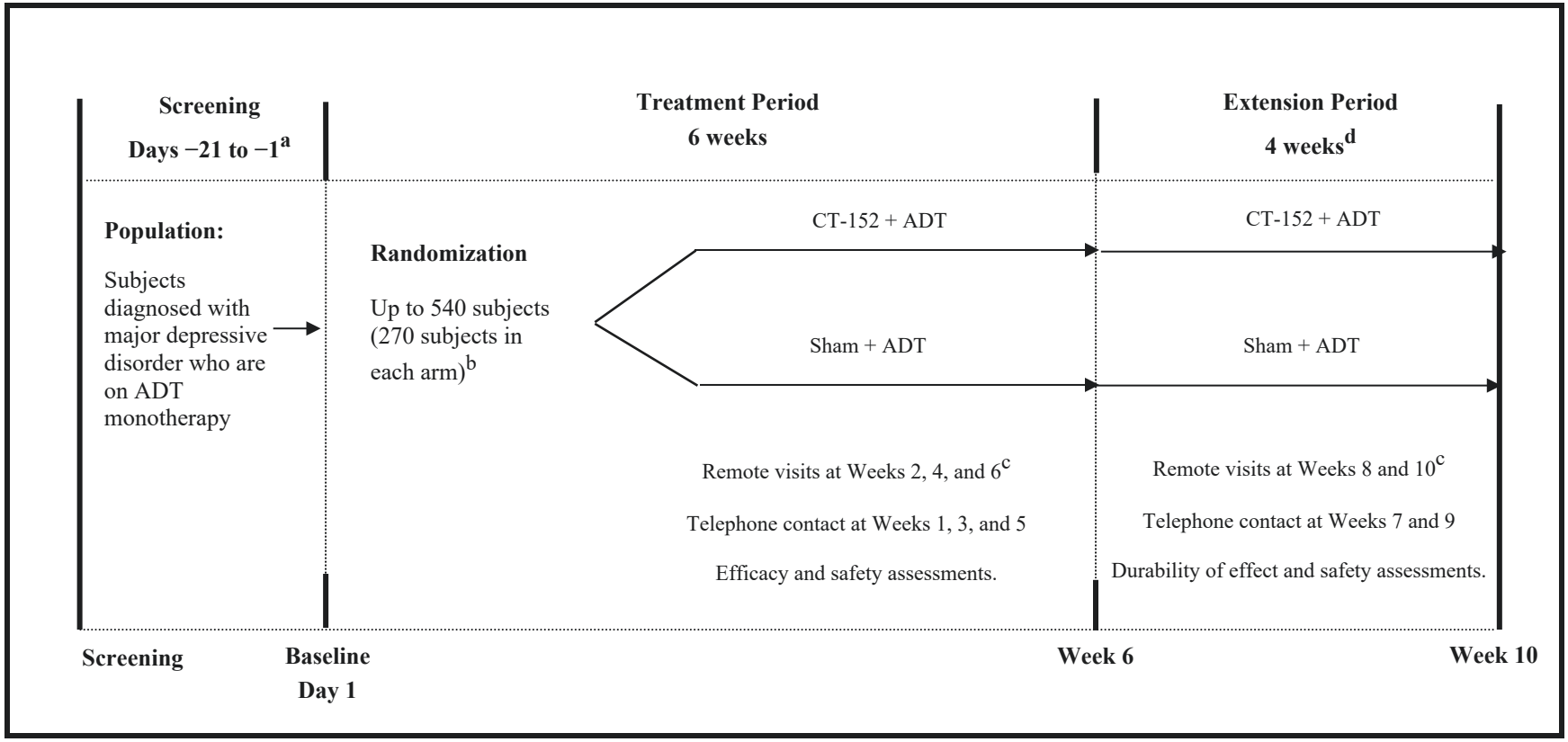

Figure 1.2-1 Trial Design Schematic

ADT = antidepressant therapy.
Note: All visits will be performed remotely. The screening visit may be performed in person at the discretion of the investigator.

[a]The subject's understanding of, and interest in, the trial will be demonstrated through adequate adherence to onboarding requirements. This will be assessed by the investigator via confirmation with the subject and completion of tasks by the subject CCI during the allotted 3-week screening window.

[b]The initial sample size is 360 subjects randomized in total. The final sample size could be increased to 540 subjects (270 subjects in each arm) as per recommendation of the Data Monitoring Committee.

[c]If deemed necessary by the investigator, additional evaluations may also be performed at an unscheduled visit either remotely or in person.

[d]After Week 6, subjects will continue participation in the trial during the extension period (Weeks 7 to 10). In the extension period, the digital mobile applications will remain installed for each group. Subjects will receive brief SMS messages reminding subjects of the previously completed CT-152 or sham treatment courses, and will continue their ADT.

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Period	Screening[a]	Treatment Period							Extension Period[b]				Notes
Trial Day (Week)	Day −21 to Day −1	Day 1 (Baseline)	Day 7 W1	Day 14 W2	Day 21 W3	Day 28 W4	Day 35 W5	Day 42 W6	Day 49 W7	Day 56 W8	Day 63 W9	Day 70 W10[c]	
Remote visit via telemedicine technology[d, e]	X[a]	X		X		X		X[f]		X		X[g]	
Telephone contact[d]			X		X		X		X		X		
ENTRANCE/HISTORY													
Informed consent	X[h]												Section 10.1.2
Demographics and medical history	X												Section 8
Psychiatric history and diagnosis	X												Section 8
Substance usage history and alcohol use disorders history	X												Section 8 Section 8.4.7
DSM-5 diagnosis of MDD	X												Section 8 Section 8.4.6
M.I.N.I	X												Section 8.4.3
Eligibility criteria	X	X											Section 5.2 Section 8

Table 1.3-1 Schedule of Assessments

Period	Screening[a]	Treatment Period							Extension Period[b]				Notes
Trial Day (Week)	Day −21 to Day −1	Day 1 (Baseline)	Day 7 W1	Day 14 W2	Day 21 W3	Day 28 W4	Day 35 W5	Day 42 W6	Day 49 W7	Day 56 W8	Day 63 W9	Day 70 W10[c]	
CCI	CCI												CCI
Confirm ADT use[i]	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.1.2 Section 6.5
ATRQ	X												Section 8 Section 8.4.4
HAM-D$_{17}$	X	X											Section 8.4.5
Randomization		X											Section 5.1
EFFICACY													
MADRS (independent rater)		X		X		X		X		X		X	Section 8.1.1
CGI-S		X		X		X		X					Section 8.1.3
PHQ-9	X					X		X					Section 8.1.4
GAD-7		X		X		X		X		X		X	Section 8.1.2
WHODAS 2.0		X						X					Section 8.1.5
CCI													
CCI													
CCI													

Table 1.3-1 Schedule of Assessments

Period	Screening[a]	Treatment Period							Extension Period[b]				Notes
Trial Day (Week)	Day −21 to Day −1	Day 1 (Baseline)	Day 7 W1	Day 14 W2	Day 21 W3	Day 28 W4	Day 35 W5	Day 42 W6	Day 49 W7	Day 56 W8	Day 63 W9	Day 70 W10[c]	
SAFETY													
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
C-SSRS	X	X		X		X		X		X		X	Section 8.2.2.1
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	Section 8 Section 6.5.1
OTHER PROCEDURES													
Download digital mobile application	X												Section 6.1.1
Urine drugs-of-abuse screen	X												Section 8.4.7
Pregnancy test	X												Section 8.4.8 Section 10.3
Adherence check (use of digital mobile application)			X	X	X	X	X						Section 6.4
Duplicate subject check	X												Section 8
Subject debriefing[k]												X	Section 6.3 Section 8

ADT = antidepressant therapy; ATRQ = Antidepressant Treatment Response Questionnaire; CGI-S = Clinical Global Impressions-Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; CCI ; *DSM-5 = Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition; CCI ; GAD-7 = Generalized Anxiety Disorder-7; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; CCI ; MADRS = Montgomery-Asberg Depression Rating Scale; M.I.N.I = Mini International Neuropsychiatric Interview; PHQ-9 = Patient Health Questionnaire-9; W = week; WHODAS = World Health Organization Disability Assessment Schedule.

Note: Shaded cells indicate trial days that subjects will be contacted by telephone by the trial site.

[a]The subject's understanding of, and interest in, the trial will be demonstrated through adequate adherence to onboarding requirements. CCI The screening visit may be performed in person at the discretion of the investigator.

[b]After Week 6, subjects will continue participation in the trial during the extension period (Weeks 7 to 10). In the extension period, the digital mobile applications will remain installed for each group. Subjects will receive brief SMS messages reminding subjects of the previously completed CT-152 or sham treatment courses, and will continue their ADT.

[c]The end of the trial will be Week 10.

[d]All remote visits via telemedicine technology and telephone contacts after baseline have a ± 3 day window to allow for variations in subject schedules and for weekends.

[e]If deemed necessary by the investigator, additional evaluations may also be performed at an unscheduled visit either remotely or in person.

[f]For subjects who discontinue early before Week 6, the procedures designated for Day 42 (including subject debriefing) will be obtained at an early termination visit occurring as soon as possible after the last use of CT-152 or sham.

[g]For subjects who discontinue early from the trial but after Week 6, the procedures designated for Day 70 will be obtained at an early termination visit occurring as soon as possible after the last use of CT-152 or sham.

[h]Electronic informed consent may be completed the day of, or prior to, the screening visit.

[i]At the screening visit, ADT use should be confirmed per the eligibility criteria. For all other visits, the ADT compliance should be checked.

[j]Adverse events will be collected from the signing of the informed consent document through the last subject visit or contact. Serious adverse events will be collected from the signing of the informed consent through and including 28 calendar days after the last use of CT-152 or sham.

[k]Subject debriefing will occur at the conclusion of a subject's participation in the trial and after all final visit procedures have been completed.

2 Introduction

CT-152 is a prescription digital therapeutic intended for the treatment of major depressive disorder (MDD) in adults. It is intended for use as an adjunct to standard of care (pharmacotherapy) and under the supervision of a clinician. The current trial is designed to provide data regarding effectiveness and safety for CT-152.

CT-152 is being co-developed by Otsuka Pharmaceutical Development & Commercialization, Inc. and Click Therapeutics, Inc.

This trial will evaluate the effectiveness of CT-152 in reducing depressive symptoms in adult subjects diagnosed with MDD who are on antidepressant therapy (ADT) monotherapy. CT-152 delivers an interactive, software-based intervention featuring cognitive-emotional training, psychotherapy lessons, psychotherapy messages, and engagement messages. CT-152 will be evaluated relative to a sham arm which will serve as a control that deploys only a working memory exercise. In order to retain the placebo nature of the sham, it will not include psychotherapy content.

Abbreviations used are listed in Section 10.5.

2.1 Trial Rationale

The current trial is designed to test CT-152 relative to a sham in a randomized, controlled trial with an adequate sample size of subjects diagnosed with MDD who are on ADT monotherapy. This trial will extend the findings from earlier monotherapy trials and ultimately provide data regarding the efficacy and safety of this software treatment. If demonstrated to be effective, CT-152 may be considered a novel, psychiatric digital therapeutic option for patients diagnosed with MDD.

2.2 Background

A 2017 World Health Organization publication *Depression and Other Common Mental Disorders: Global Health Estimates* reported 322 million people across the globe, 4.4% of the world's population, are living with depression.[1] In a large 2018 United States (US) national survey, prevalence estimates for *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (*DSM-5*) MDD were even higher with 12-month and lifetime prevalence of MDD reported at 10.4% and 20.6%, respectively, with most having moderate (6 - 7 symptoms) or severe (8 - 9 symptoms) MDD that was associated with comorbidity and impairment.[2] Major depressive disorder has a severe impact on overall functioning[3] and is a leading cause of disability worldwide in terms of total years lost due to disability.[4] Based on data from 2010, depression-related expenditures in the US were

greater than $210 billion, with employers incurring $102 billion in losses due to absenteeism, presenteeism, and disability, and direct medical costs of $99 billion.[5] There is a critical need to improve treatment outcomes associated with major depression.[6]

Major depressive disorder, per *DSM-5*, is defined by 5 criteria: (A) the presence of ≥ 5 symptoms to be present within a 2-week period, (B) The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, (C) The episode is not attributable to the physiological effects of a substance or to another medical condition, (D) The occurrence of a major depressive episode (MDE) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders and (E) There has never been a manic episode or a hypomanic episode.[7]

Criteria A to C above represent a MDE.[7] Primary symptoms of MDE are depressed mood or anhedonia (loss of interest or pleasure), while secondary symptoms of MDE include appetite or weight changes, sleep difficulties (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate, feelings of worthlessness or excessive guilt, and suicidality.[7] Each symptom is rated in all or none (1 or 0), with the total symptom score determining the presence (or the absence) of MDE.[8] Depending on the number and severity of symptoms, MDE may be specified as mild, moderate, or severe.[9]

The American Psychiatric Association recommends healthcare providers select from various treatment modalities treatment in the acute phase to target remission of the MDE and return the patient to the level of functioning prior to the MDE.[10] Currently available options include ADT, depression-focused psychotherapy (eg, cognitive behavioral therapy [CBT]), ADT and psychotherapy combination treatment, or other somatic therapies (eg, electroconvulsive therapy (ECT), transcranial magnetic stimulation).[10] Clinical features (eg, symptom severity, presence of co-occurring disorders or psychosocial stressors) and other factors (eg, patient preference, prior treatment experiences) influence clinician selection of an initial treatment modality.[10] In most patient populations, when ADT is indicated and psychotherapy is an available and practical option, combining ADT and psychotherapy often provides the quickest and most sustained response.[11,12] Combination therapy also appears to provide significantly higher improvements in depression symptoms, improvement in quality of life, and increased compliance with treatment.[13]

Despite major professional society treatment guidelines, unmet needs remain in the treatment of MDD. Firstly, many patients with MDD do not receive adequate treatment due to a variety of barriers (eg, shortage and uneven geographic distribution of trained providers[10,14,15,16] time gaps seeing a provider[17] and patient preferences[18]). Secondly, even when patients receive adequate treatment, many have a suboptimal response.[19,20,21,22] Therefore, novel, clinically validated and easily accessible monotherapy and augmentation treatment options are needed to treat depression. Emerging technologies may help address some of these unmet needs and digital therapeutics are one such option. A digital therapeutic is defined as an evidence-based therapeutic intervention to patients that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease.[23] Since digital therapeutics can include evidence-based psychotherapy as well as interventions targeting aberrant neural circuits for specific diseases[10,24,25,26,27,28,29] these software-based treatments can offer a new augmentation option for suboptimal responders to first-line MDD treatments.

The digital therapeutic for evaluation in this trial includes a cognitive-emotive training intervention called Emotional Faces Memory Task (EFMT) which has been shown to reduce symptoms of depression.[30,31] This treatment has been developed from a growing body of research that links MDD with impaired cognitive control for emotionally salient information.[32,33] This impaired cognitive control is thought to manifest in perseverative thinking abnormalities such as ruminating, dwelling, obsessing, and worrying.[34] These cognitive abnormalities serve to maintain or exacerbate the sad or depressed mood component of MDD.[33] Through the cognitive-emotional training exercise, EFMT aims to repair connectivity in disrupted brain circuitry observed in MDD via simultaneous emotion recognition and working memory tasks, which elicits activity in the amygdala and dorsolateral prefrontal cortex, respectively.[30,32] Data from 2 earlier randomized controlled studies support the efficacy of this software in reducing clinician-rated MDD symptom severity.[30,31] And, a recent functional MRI study involving patients from 1 of the earlier randomized controlled studies, in which subjects were scanned at baseline and post-treatment to identify changes in resting-state functional connectivity and effective connectivity during emotional working memory processing, provided initial evidence that EFMT may be associated with changes in short-term plasticity of brain networks implicated in MDD.[35]

In addition to the aforementioned cognitive and emotional deficits, depression is characterized by impairments in behavioral and social functioning that exacerbate depressed mood.[36] Symptoms include, but are not limited to, negative self-concept,

emotional dysregulation, hopelessness, behavioral avoidance, and social withdrawal.[37] Psychotherapies such as CBT[38] behavioral activation[39] and acceptance and commitment therapy[40] have demonstrated efficacy in the treatment of depression. Similarly, digital psychotherapy sessions delivered via mobile or web-based applications have likewise been shown to be effective in the treatment of depression.[41,42] A unique challenge, however, lies in the achievement of optimal user engagement and adherence to digital treatment protocols.[43,44] Automated technology, such as alerts or reminders, may assist patients to adhere to their health regimens.[45]

In summary, CT-152 consists of cognitive-emotional training delivered through the EFMT which will aim to enhance emotional information-processing to alleviate symptoms of depression.[30] In conjunction with EFMT, psychotherapy lessons and messages will target psychosocial symptoms of depression including emotion-coping deficits, behavioral and social dysfunction, and depressive cognitive biases. Complementary messages will be sent to users to encourage skills utilization in real life settings and prompt engagement through messaging. Similar to pharmacological treatment options, it is critical that the efficacy and safety of these novel treatment technologies are evaluated in randomized control trials with adequate sample size and clinically meaningful endpoints.[46,47,48] To this end, the current trial aims to assess the efficacy and safety of CT-152.

2.3 Known and Potential Risks and Benefits

Adverse events (AEs) related to mobile device use may include dizziness, fatigue, or headache. No attributable AEs were observed in previous research studying CT-152. Please refer to the CT-152 Investigator Brochure for additional risk information.

The EFMT component of CT-152 has been shown to reduce symptoms in patients experiencing a MDE on a clinically validated scale of depression. In addition, digitally-delivered psychotherapy content has been shown to be efficacious for MDD patients. Based on design intent and early feasibility research, CT-152 is intended to help patients who engage with the digital therapeutic to alleviate or reduce symptoms of MDD.

The subjects may experience some AEs due to their underlying condition or with the use of ADT. The risk profile of ADTs used in clinical practice is well understood and is detailed in the package insert of the ADT medications.

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3 Objectives and Endpoints

The trial objectives and endpoints are provided in Table 3-1.

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary objective: To compare the effectiveness of CT-152 with sham, in adult subjects diagnosed with MDD who are on ADT monotherapy.	Primary efficacy endpoint: Change from baseline to Week 6 in the MADRS total score. The durability of effect will include 3 MADRS assessments at Weeks 6, 8, and 10. CCI [redacted] Key secondary efficacy endpoint: • Change from baseline to Week 6 in the GAD-7 total score. Durability based on GAD-7 will include 3 assessments, at Weeks 6, 8, and 10, demonstrating a numerically larger improvement on point estimate of the difference in the change from baseline in GAD-7 total score at Weeks 8 and 10 in CT-152 compared to sham. Other efficacy endpoints: • Change from baseline to Weeks 2 and 4 in the MADRS total score • Change from baseline to Weeks 2 and 4 in the GAD-7 total score • MADRS response rate (≥ 50% reduction from baseline) at Weeks 2, 4, and 6. • Change from baseline to Weeks 2, 4, and 6 in the CGI-S score. • Change from baseline to Week 6 in the WHODAS 2.0 total score. • Change from screening to Weeks 4 and 6 in the PHQ-9 total score. • MADRS partial response (MADRS score reduction from baseline ≥ 30% and < 50%) at Weeks 2, 4, and 6.

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Table 3-1 Trial Objectives and Endpoints	
Objectives	**Endpoints**
	• MADRS response rate (full or partial, defined as ≥ 30% reduction in MADRS total score from baseline) at Weeks 8 and 10. CCI [redacted]
Safety objective: To evaluate the safety of CT-152 in adult subjects diagnosed with MDD who are on ADT monotherapy.	Safety endpoints: • Frequency and severity of AEs, serious AEs, and discontinuations from the trial due to AEs.

CGI-S = Clinical Global Impressions-Severity; CCI [redacted]
GAD-7 = Generalized Anxiety Disorder-7; CCI [redacted] ;
MADRS = Montgomery-Asberg Depression Rating Scale; CCI [redacted] PHQ-9 = Patient Health Questionnaire-9; WHODAS = World Health Organization Disability Assessment Schedule.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This is a multi-center, randomized, controlled trial to evaluate the effectiveness of CT-152 in adult subjects diagnosed with MDD who are on ADT monotherapy for the treatment of depression.

The primary objective of the trial is to evaluate the effectiveness of CT-152 in reducing depressive symptoms compared with sham which will serve as a control. The primary efficacy endpoint is the change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. The key secondary efficacy endpoint for the trial is the change from baseline to Week 6 in the Generalized Anxiety Disorder-7 (GAD-7) total score. The other efficacy endpoints will include the evaluation of the MADRS, GAD-7, Clinical Global Impression – Severity (CGI-S), World Health Organization Disability Assessment Schedule (WHODAS) 2.0, and Patient Health Questionnaire-(PHQ-9) at Weeks 2, 4, and/or 6. To evaluate the durability of the effect of CT-152, the change from baseline to in MADRS and GAD-7 total score as well as

MADRS response rate will be evaluated at Weeks 8 and 10. Further details are provided in Table 3-1.

Subjects will participate in the trial for up to 13 weeks. The trial will include a screening period of up to 3 weeks, a treatment period for 6 weeks, and an extension period for 4 weeks.

Eligible subjects will be randomized to 1 of 2 digital mobile applications (CT-152 or sham) on Day 1.

To mitigate subject expectation, subjects in this trial will be blinded to the efficacy hypothesis. Eligible subjects will be informed by trial site staff that a) they will participate in the trial for up to 13 weeks 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 ADT. Both treatment arms will be presented as possibly helping to improve MDD. No references to CT-152 or sham should be made to the subject. At the conclusion of a subject's participation in the trial, and after all final visit procedures have been completed, trial site staff will inform the subject of the trial hypothesis, ie, that one digital therapeutic was hypothesized to be more beneficial in improving depression symptoms, but there was a need for a trial to confirm. Trial site staff will be provided with debriefing guidelines to assist in this discussion with the subject. See Section 6.3 Measures to Minimize/Avoid Bias.

Trial site staff will implement procedures either by telephone or remote visit via telemedicine technology, at all visits. The screening visit may be performed in person at the discretion of the investigator. A trial site may conduct an unscheduled visit in person or remotely at any time if needed to assess a safety issue/concern.

Remote visits will be conducted using a sponsor-designated telemedicine platform with a portal accessible by the trial site staff, and subjects will be asked to download a mobile application (separate from the investigational digital mobile application) in order to provide consent to the trial and complete trial assessments, including self-administered scales.

Prior to downloading the mobile application for conducting telemedicine visits, subjects will be asked to provide consent to participate in a registry and agree to its privacy policy and terms of service required to collect subjects' information within the telemedicine platform, including identity verification. Subjects will be required to complete the identity verification process remotely before they can electronically sign the trial consent in order to comply with 21 Code of Federal Regulations (CFR) Part 11 electronic signature requirements. Details are found in the Site Operations Manual.

The screening period begins after informed consent has been obtained. Subjects who fulfill entry criteria at the screening visit will download the digital mobile application on their smartphone and receive access to an onboarding software module. A call center can assist with the downloading of the digital mobile application. During the screening period, subjects will become familiar with the software. The subject's understanding of, and interest in, the trial will be demonstrated through adequate adherence to onboarding requirements. This will be assessed by the investigator via confirmation with the subject and completion of tasks by the subject CCI during the allotted 3-week screening window.

Following the screening visit, subjects will be considered eligible based upon the following:

- Adherence and performance on the onboarding software module by the subject CCI
- Continuing to meet all inclusion and no exclusion criteria based on investigator assessment.

On Day 1, the eligible subjects will be randomized 1:1 (CT-152 or sham) across approximately 50 trial sites in the US. The sample size at any single trial site will be capped at approximately 15% of the total subjects randomized into the trial. Randomization will be stratified by trial site.

During the treatment period (Day 1 [baseline] to Week 6) subjects will have a remote visit at Weeks 2, 4, and 6 and will be contacted by telephone by the trial site at Weeks 1, 3, and 5. Subjects will be expected to be adherent with their digital mobile application exercises during the treatment period.

After Week 6, subjects will continue participation in the trial during the extension period (Weeks 7 to 10). In the extension period, the digital mobile applications will remain installed for each group. Subjects will continue to receive brief short message service (SMS) messages reminding subjects of the previously completed CT-152 or sham treatment courses (see Section 6.1.1 for further details), and will continue their ADT. Subjects will have a remote visit at Weeks 8 and 10 and will be contacted by telephone by the trial site at Weeks 7 and 9.

The end of the trial will be Week 10.

During the treatment and extension periods, a blinded and independent expert clinical rater from a centralized vendor, who will otherwise not interact with the subject, will rate

and record the MADRS remotely by telephone while remaining blinded to treatment assignment and other clinical information. This may occur separately from the remote trial site visit but must be performed within the window described in the schedule of assessments (Table 1.3-1).

The CGI-S scale will be completed by designated trial site staff at remote visits that occur during the treatment period. Other assessments to be performed during the trial include the GAD-7, WHODAS 2.0, PHQ-9,CCI

During the trial, the trial site staff will administer the Columbia-Suicide Severity Rating Scale (C-SSRS), review subject adherence to the treatment sessions during the treatment period, confirm subject adherence to their current ADT, and assess AEs and concomitant medications.

4.2 Scientific Rationale for Trial Design

In clinical practice the digital therapeutic is to be used in the context of prescription under clinical supervision by patients receiving ADT; thus, regular bi-weekly interactions with the trial site are scheduled, which include procedures to discuss engagement with the product and protocol adherence (treatment period only), AEs, and concomitant medications.

As the content of CT-152 and sham differs and discussion of the content could unblind trial site staff, blinded ratings will be conducted for the primary efficacy endpoint assessment by centralized raters who have no access to trial data or clinical information other than what is solicited for this assessment (see Section 6.3 Measures to Minimize/Avoid Bias for further information). Subjects will be assessed based on standard clinician-rated and subject-rated outcome scales for depression and anxiety during the treatment period. In addition, in order to minimize potential expectation effects, subjects will be informed that either one of the two randomized treatments may improve symptoms of depression.

To evaluate durability of effect, the trial will include a 4-week extension period for all subjects. During the extension period, subjects will continue to receive SMS messaging and will continue their ADT.

4.3 Dosing Rationale

Not applicable.

4.4 End of Trial Definition

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

4.5 Definition of Completed Subjects

Subjects who are evaluated at their last scheduled visit will be defined as trial completers. For purposes of this trial, subjects who complete the Trial Day 70 assessments will be defined as trial completers.

5 Trial Population

5.1 Subject Selection and Numbering

All subjects will be given a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits] upon providing consent) and the site number will be designated by the sponsor. CCI [redacted]

Subjects will be randomized into the trial on Day 1 provided they have satisfied all entry criteria at the screening and baseline visits. A subject must meet all eligibility requirements at the screening and baseline visits prior to randomization. Randomization will be stratified by trial site. Eligible subjects who are enrolled in the trial will be assigned a unique subject randomization number for digital mobile application assignment at baseline. Results of the eligibility assessment, date of randomization, and randomization number will be recorded in eSource.

Allocation of subjects to CT-152 or sham will proceed through the use of a randomization system. Once subject screening numbers and randomization numbers have been assigned, they cannot be reassigned or reused for any reason. Specific instructions for use of the randomization system will be provided under separate cover. The randomization list by trial site will be blocked and randomly sized to balance in changes over time in the eligible population. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject will be masked on any material received by the sponsor.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether this protocol is suitable for each subject.

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's trial team before subjects are included in the trial. There must be evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the trial prior to any trial procedure being performed. Subjects must be willing and able to comply with scheduled remote visits and telephone contacts, treatment plan, urine test for drugs-of-abuse, and other trial procedures.

Trial sites are required to communicate certain aspects of subject data during the screening period [redacted] as detailed in the Site Operations Manual. An assessment on inclusion and exclusion criteria will be made to determine the subject's eligibility [redacted] approve subject eligibility in order for the subjects to be randomized. Subjects cannot be enrolled until trial site personnel have received the final [redacted] notification from the medical monitor or clinical scientist.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

1) Male or female subjects aged 22 to 64 years old at the time of informed consent.
2) Fluent in written and spoken English (confirmed by ability to read and comprehend the informed consent form [ICF]).

3a) A current primary diagnosis of MDD based on the criteria in the *DSM-5*, single or recurrent episode, without psychotic features and do not meet criteria for MDD with mixed features subtype, and on ADT monotherapy. If other allowable psychiatric diagnoses are present, they must not be considered primary (causing a higher degree of distress or impairment than MDD).

3b) Subjects must be in a current MDE, as defined by *DSM-5* criteria and confirmed by both the Mini International Neuropsychiatric Interview (M.I.N.I) and an adequate clinical psychiatric evaluation.

4) A score of Hamilton Rating Scale for Depression, 17-item ($HAM\text{-}D_{17}$) ≥ 18 at screening and the baseline visit (Day 1).
5) Subjects must have a reported history for the current episode of inadequate response to their current monotherapy ADT. Treatment with the current ADT must be of adequate dose and duration, defined as at least 6 weeks at a minimum therapeutic dose (or higher) according to the Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire (MGH-ATRQ) performed at screening. Inadequate response is defined as < 50% reduction in depression symptom severity per the MGH-ATRQ. Additionally, the subject must be on a stable dose of their current monotherapy ADT for a minimum of 4 weeks prior to baseline (Day 1).

6) Subjects who are willing to maintain ADT treatment at the current dose for the duration of their participation in the trial.
7) Subjects and the clinician are able to confirm a calendar of remote visits and telephone contacts.
8) Subjects who are the only users of an iPhone with iPhone operating system (iOS) 13.0 or greater capabilities, or a smartphone with an Android operating system (OS) 9.0 or greater capabilities, and agree to download and use the digital mobile application as required by the protocol.
9) Subjects who are willing and able to receive SMS text messages and push messages on their smartphone.
10) Subjects who, in the opinion of the investigator, will not require additional pharmacological intervention during the trial for the treatment of depression.
11) Subjects who have successfully completed the onboarding software module in the digital mobile application during the screening period.
12) Subjects who continue to consent to participate in the trial and are judged to understand the use of the digital mobile application at the baseline visit (Day 1).

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

1) Subjects who are trial site staff members or employees directly involved in the conduct of the trial.
2) Subjects with a reported inadequate response to > 1 adequate trial of ADT for the current episode. An adequate trial is defined as at least 6 weeks at a minimum therapeutic dose (or higher) according to the MGH-ATRQ. Inadequate response is defined as < 50% reduction in depression symptom severity per the MGH-ATRQ.
3) Subjects who have been treated with psychopharmacological augmentation for depression in the past or in the current episode (eg, lithium, triiodothyronine, or antipsychotics added to ADT, multiple ADTs). If, in the clinical opinion of the investigator, the subject did not receive an adequate trial of an agent used for augmentation, these subjects may be considered for inclusion following discussion and approval by the medical monitor.
4) Subjects who are currently receiving or have received psychotherapy within 90 days prior to screening.
5) Subjects who have failed to respond to an adequate course (≥ 8 weeks) of CBT at any time in the past.
6) Suicidality assessment:
    - Subjects who answer “Yes” on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) within the last 12 months prior to screening or at the baseline visit (Day 1), OR

- Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) within the last 12 months prior to screening or at the baseline visit (Day 1), OR
- Subjects who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or suicidal behavior) within the last 24 months prior to screening or at the baseline visit (Day 1), OR
- Subjects who, in the opinion of the investigator, presents a serious risk of suicide.

7) Subjects who at any time in the past have been treated with ECT or neuro-modulation devices (transcranial magnetic stimulation, vagus nerve stimulation, or transcranial direct current stimulation, etc) for depression.
8) Subjects who have at any time in the past received ketamine, esketamine, or arketamine for treatment of depression.
9) Subjects who are currently using a computer, web, or smartphone software-based application or equivalent for mental health or depression. Subjects who agree to discontinue use at screening will be permitted to enter the trial.
10) Subjects who have a current diagnosis of substance or alcohol use disorder (excluding nicotine) per *DSM-5* criteria within 6 months prior to the screening visit.
11) Subjects with a positive urine drug screen for illicit drugs or prohibited medications are excluded. Subjects with a positive urine drug screen resulting from use of cannabis, or prescription or over-the-counter medications, or products that, in the investigator's documented opinion, do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor. Additionally, the investigator may retest the subject if it is believed the positive urine drug screen is a false positive test, following discussion with the medical monitor.
12) Subjects in a current MDE lasting longer than 2 years.
13) Subjects who are considered resistant/refractory to treatment by history and per investigator judgment.
14) A lifetime diagnosis of schizophrenia, schizoaffective disorder, other psychotic disorder, or Bipolar I/II disorder, or current posttraumatic stress disorder, panic disorder, or obsessive-compulsive disorder, as assessed by the M.I.N.I.
15) Current generalized anxiety disorder or social anxiety disorder as assessed by the M.I.N.I and considered to be primary (causing a higher degree of distress or impairment than MDD).
16) Subjects diagnosed with any *DSM-5* personality disorder as assessed by the investigator during the psychiatric evaluation and/or from medical records.
17) Depression due to a general medical condition or a neurologic disorder.
18) History of seizure disorder other than a single childhood febrile seizure that fully resolved.

19) Subjects who would be likely to require prohibited concomitant therapy during the trial.
20) Female subjects of childbearing potential with a confirmed positive pregnancy test result after signing the informed consent and before the baseline visit on Day 1.
21) Participation in other clinical research trials (interventional or observational) involving investigational drugs or devices within 180 days prior to randomization and/or during trial participation, or who have participated in more than 2 clinical trials within the past year.
22) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness.
23) Subjects who, in the opinion of the investigator, sponsor, or medical monitor, should not participate in the trial.

Subjects must agree to restrictions to medications and lifestyle as described in Section 6.5.1 and Section 5.3, respectively.

5.3 Lifestyle Considerations

Since this is a trial of a digital mobile application, subjects must, in their work and home life, have routine access to their smartphones. In addition, they will be required to attend remote visits during the trial. This will be included in the informed consent and reiterated in the discussion of consent with the subjects.

Subjects should refrain from using alcohol during the times the digital mobile application will be accessed.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not randomized or assigned trial treatment.

Subjects who sign an ICF but who are not randomized to CT-152 or sham are permitted to be rescreened after consultation with the sponsor clinician or medical monitor. In the event that the subject is rescreened for trial participation, a new ICF must be signed, a new ID number obtained, and all screening tests and procedures must be repeated. A subject may not rescreen more than once.

Screen failures previously excluded for a positive drug screen for illicit drugs or prohibited medications are not eligible to be rescreened. If a subject meets the definition of a screen failure in this trial, the following information will be recorded in eSource:

- Date of informed consent

- Visit date (screening visit)
- Demographics (collection date, date of birth, sex, race, ethnicity)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure

6 Trial Treatments

6.1 Trial Treatments Administered

6.1.1 Digital Therapeutic

For information regarding the trial design, see Section 4.1.

Subjects that meet all the initial inclusion criteria and none of the exclusion criteria at screening will download and install the digital mobile application onto their own smartphone device that they will use for the trial. A dedicated call center can assist with the initial downloading of and access to the digital mobile application. The investigator will confirm the subject's understanding of, and interest in, the trial through adequate adherence to the run-in onboarding requirements in the onboarding software module CCI during the 3-week screening period (Day −21 to Day −1).

The onboarding software module will provide example cognitive control task sessions. The content of these example sessions will not include therapeutic content, so as to minimize bias once subjects are randomized to 1 of the 2 arms (CT-152 or sham).

At the baseline visit (Day 1), successful use of the onboarding software module will be confirmed. Success is defined as completing 3 example sessions CCI during the screening period and achieving a difficulty level of 2 or greater in the cognitive control task. An adherence check will be documented in eSource. CT-152 or sham will be activated within the digital mobile application during the baseline visit with an access code.

CT-152 delivers an interactive, software-based intervention featuring cognitive-emotional training, psychotherapy lessons, psychotherapy messages, and engagement messages. Each treatment session will consist of an EFMT exercise and a psychotherapy lesson. Sham will serve as a control.

Sham will provide a cognitive training exercise designed to retain user interest while minimizing any therapeutic effect. Each treatment session will consist of a Shapes

Memory Task (SMT) exercise. It will present users with an analogous structure, matched for time and attention to the cognitive-emotional training exercise found in CT-152. In order to retain the intended placebo nature of the sham, it will not include EFMT or psychotherapy content.

The intervention will begin the same day as the baseline visit, once the baseline visit has been completed. The subjects will progress through a treatment schedule of 18 sessions (approximately 30 - 45 minutes) at a rate of 3 sessions per week over the 6-week treatment period (Day 1 [baseline] to Week 6).

After Week 6, subjects will continue participation in the trial during the extension period (Weeks 7 to 10). In the extension period, the digital mobile applications will remain installed for each group with EFMT and SMT no longer available. Psychotherapy content provided previously will remain available for optional reference in the CT-152 group but no new therapeutic content will be introduced and no required treatment schedule is in place. The 2 groups will each receive brief SMS messages in the extension period reminding subjects of the previously completed CT-152 and sham treatment courses.

6.1.1.1 Call Center

A dedicated call center is available to support the subject and the trial site on the initial downloading of and access to the digital mobile application, as well as any technical issues with the digital mobile application throughout the trial.

Subjects must be instructed by the investigator to contact the call center with any technical questions about the digital mobile application. All calls to the call center will be documented and processed. Basic user technical issues will be resolved by the call center.

If a subject contacts the call center with an AE, the call center will log the call and immediately provide this information to the trial site and sponsor or sponsor's designee for follow-up per Section 8.3.

If a subject contacts the call center with a possible or suspected product quality complaint (PQC), the call center will log the call. All call records (tickets) captured by the call center will be provided to the Click Therapeutics Quality Team for PQC analysis, tracking, and resolution per Section 6.2.2.

If a subject reports a possible or suspected PQC to the investigator or designee during a remote visit or telephone contact, the investigator or designee is to immediately contact the call center, which will log the call and immediately provide the information to the Click Therapeutics Quality Team per Section 6.2.2.

In addition to call tracking, calls with the call center may be recorded for quality purposes. Call center contact information and processes are detailed in the Site Operations Manual.

6.1.2 Antidepressant Therapy

To qualify for this trial, subjects must have received adequate treatment (ie, minimum therapeutic dose or higher) with a permitted ADT in the current episode for at least 6 weeks prior to screening. The medications listed in Section 6.5.2 are considered permitted ADT. Additionally, the subject must have received the same dose of their current monotherapy ADT for at least 4 weeks prior to baseline (Day 1). Subjects who are taking ADTs other than the permitted ADTs will not be eligible for the trial.

Subjects who are eligible for randomization will be randomized into the trial and will receive either CT-152 or sham in addition to their current ADT during the treatment period. During the extension period, subjects will continue their ADT.

Subjects must remain on the same ADT and should remain on the same dose for the duration of their participation in the trial. However, if the principal investigator or designee determines that dose adjustments to ongoing ADT must be made for tolerability reasons, this requires discussion with the medical monitor to document the reason for the change. In all cases, the specific ADT cannot change before the end of the trial and at all times the dose of permitted ADT must remain within the therapeutic range specified in the drug label. If subjects cannot tolerate the minimum therapeutic dose of ADT they must be discontinued.

Subjects required to change from one ADT to another, or who require augmentation with additional pharmacotherapy or psychotherapy as part of ongoing clinical care during the course of the trial, must be withdrawn. Additionally, treatment with more than one ADT during the trial, or other pharmacological augmentation, is not permitted.

Subjects are expected to maintain the ADT formulation identified at trial entry (ie, generic or branded) throughout their participation in the trial. The supply for the ADT can be provided by the sponsor via a mail order pharmacy or the subject can continue to take ADT that was previously prescribed before trial entry.

If the subject does not continue to take ADT from the supply that was previously prescribed before trial entry, the ADT will be prescribed by the principal investigator or designee and filled by a mail order pharmacy and delivered to the subject's home. Details are provided in the Site Operations Manual.

Subjects should maintain the type of ADT (generic or branded) during the trial period as before trial entry, regardless of the source of ADT supply.

6.2 Management of CT-152 and Sham

Once the subject is randomized, the investigator will make sure that the subject has properly set up the digital mobile application on their smartphone device. The subjects should be instructed to make sure they have their smartphone device with them and that they keep their smartphone device adequately charged during scheduled remote visits. The trial site staff will review the schedule of remote visits, telephone contacts, and weekly required use of the digital mobile application with the subjects. Subjects must be advised not to discuss or share their investigational treatment with others, including any trial site staff and the independent rater.

6.2.1 Returns and Destruction

Upon completion of Week 10 or early termination of the trial, the subject will be asked to uninstall the digital mobile application from their smartphone device.

6.2.2 Reporting of Product Quality Complaints and Product Nonconformance

A PQC is any written, electronic, or oral communication by a CCI, consumer, subject, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, reliability, safety, durability, effectiveness, or performance of a medical device or a falsified, tampered, or diverted product after it is released for distribution.

Examples include, but are not limited to, communications involving failure/malfunction of a medicinal product or medical device to meet any of its specifications.

An investigational product nonconformance is the nonfulfillment of a specified product requirement during a clinical trial.

For this trial, all PQCs related to the digital mobile application (CT-152 or sham) are reportable. Any PQCs reported that are associated with the ADTs should be reported by the subject to the prescribing physician, pharmacist, and/or site investigator as appropriate.

6.2.2.1 Eliciting and Reporting Product Quality Complaints and Product Nonconformance

During the trial, possible or suspected digital mobile application PQCs will be gathered by the call center as it processes technical support calls as described Section 6.1.1.1.

Whether the call is from a subject, trial site personnel, or sponsor, all calls and issues will be tracked. Simple technical issues will be resolved and marked as such. Issues determined to be possible or suspected PQCs will be transferred immediately to the Click Therapeutics Quality Team, which will follow its quality management system (QMS) processes for determining, investigating, and resolving PQCs. The Click QMS includes careful review of all reported issues, including those identified as product nonconformances, and incorporation of same into the product design records. Traceability between the call center system and the Click QMS will be maintained.

The investigator or designee must report all possible or suspected PQCs identified from the subject from the time of download of the digital mobile application, through the end of the subject's trial participation. The investigator or designee must notify the call center within 24 hours of becoming aware of the possible or suspected PQC. Call center contact information and processes are detailed in the Site Operations Manual.

6.2.2.2 Information Required for Reporting Purposes

- Description of complaint or nonconformance
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, phone number, e-mail address)
- Identification of material (product/compound name)
- Clinical protocol reference (number and/or trial name)

6.2.2.3 Return Process

The digital mobile application will be uninstalled as described in Section 6.2.1.

6.2.2.4 Assessment/Evaluation

Assessment and evaluation of digital mobile application malfunctions will be handled by the sponsor, with support from the Click Therapeutics Quality Team.

6.3 Measures to Minimize/Avoid Bias

Procedures for breaking the blind can be found in Section 8.3.3.

Subjects participating in this trial will be blinded to the efficacy hypothesis of the trial. Both treatment arms will be presented to the subject as possibly effective in treating symptoms of MDD. No references to CT-152 or sham will be made to the subject.

The purpose of this approach is to limit the risk of subject unblinding to treatment assignment and expected efficacy. If the subject believes that both arms are possibly effective, they are less likely to question the efficacy of the treatment in which they were

assigned. This may increase subject adherence to treatment and reduce the overall risk of unblinding. In all subject facing documentation (ICF, informational brochures, etc.) neither CT-152, nor the sham will be named. Instead, reference will only be made to "digital therapeutic". This approach is limited to interventions that propose minimal risks, where withholding information will not adversely affect the subjects' rights and welfare, and where the trial cannot practicably be carried out without withholding the information from the subject.

Potential investigator or trial site staff unblinding to the trial arms, which may occur during discussions between the subject and trial site staff, would not impact the MADRS assessments (primary efficacy endpoint as well as included in the other/additional efficacy endpoints) which will be collected by the blinded and independent rater who does not have knowledge of the intervention being evaluated. This rater is managed by a centralized vendor external to the trial site. In order to protect blinding, the investigator and trial site staff will be trained not to provide any information to the independent rater, the subject, or the sponsor regarding the trial arms. 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.

A blinded and independent expert clinical rater, who will otherwise not interact with the subject, will rate and record the MADRS as described in Section 4.1. The independent rater and subjects will be trained to avoid discussion of the content of the digital mobile application the subject receives or any other aspect of the trial participation. Any potential unblinding at the independent rater level may trigger replacement of the rater. All instances of unblinding of the independent rater during the trial will be recorded.

To further minimize potential bias, trial sites will designate at least 1 individual to administer the other efficacy endpoint assessments. This individual will not do adherence checks with the subject, and should have limited contact with the subject outside of the assessments. Trial sites should take steps to ensure this individual is not unblinded, even if the investigator or other trial site staff are.

All subjects in the trial will complete subject-reported outcomes independently and will interact with the trial site staff only to ensure completeness of the scale or clarity of its administration. Moreover, these procedures will be consistent across the CT-152 and sham groups, thus, there is no anticipated difference between groups in assessing adherence and the frequency of unblinding that could bias results in either direction.

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6.4 Adherence to Digital Therapeutic

6.4.1 Definitions of Adherence

During the treatment period only, all randomized subjects will be instructed to complete 3 treatment sessions per week over a period of 6 weeks, for a total of 18 treatment sessions.

For subjects in the CT-152 arm, each treatment session will consist of 2 components: an EFMT exercise and a psychotherapy lesson. Each EFMT exercise consists of 15 rounds. The EFMT exercises and psychotherapy lessons must be completed in sequence.

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6.4.2 Adherence Messaging

The digital mobile application will send messages to the subject to encourage them to remain engaged during the treatment period.

Subjects who miss an individual digital mobile application session during the treatment period will receive automated adherence reminder messages on their mobile device. These may be delivered via push notification or text message.

6.4.3 Adherence Monitoring

It is important to routinely check whether the subject has been adherent to completing the sessions on the digital mobile application during the treatment period as required per the protocol. Adherence checks will be performed during the treatment period only. The schedule of assessments (Table 1.3-1) includes adherence checks during the Week 1, 3, and 5 telephone contacts by the trial site and the Week 2 and 4 remote visits. There is no treatment schedule and no adherence requirements for the extension period.

The adherence checks are intended to identify subjects at risk of becoming 'nonadherent' and provide the investigator an opportunity to intervene as early as possible to maximize adherence across the trial.

Weekly adherence data will be obtained by the trial site staff during remote visits and telephone contacts in an adherence code read from the subject's mobile device. The code is calculated by the digital mobile application according to the definition of adherence in Section 6.4.1. The code will indicate to the investigator whether the subject has been adherent in the near term prior to the visit. Investigators will use this information to remind the subject to complete 3 sessions a week during the treatment period and to identify any technical issues that might be interfering with adherence. The language to be used by the investigator and steps for addressing technical issues will be specified in the Site Operations Manual.

6.5 Prior and Concomitant Medications or Therapies

All prescription and nonprescription therapy (pharmacological or other therapy) taken during the trial will be recorded in eSource.

The start date and stop date, if applicable, for all concomitant medication and nonpsychiatric treatments and therapies received by the subject up to 30 days before screening and during trial participation will be recorded in eSource.

The start date and stop date, if applicable, for all treatment for psychiatric disorders received by the subject at any time in the past will be recorded in eSource.

The use of ADT will be confirmed at screening and throughout the trial and will be recorded in eSource.

6.5.1 Prohibited Medications or Therapies

Except for the medications listed in Section 6.5.2, the following treatments are prohibited during the noted time frames and throughout trial participation. Subjects requiring a prohibited medication to control a medical condition should not be enrolled. Investigators

may initiate appropriate medications for the treatment of AEs other than worsening of depressive symptoms. If treatment involves medications that are prohibited under this protocol, the investigator should discontinue the subject from the trial. The medical monitor should be contacted in the event of any questions.

Within 90 Days Prior to Screening:

- Psychotherapy

Within 7 Days Prior to Randomization:

- Use of sedative hypnotics (except as defined in Section 6.5.2)
- Other psychotropic drugs or substances, eg, propranolol and mood stabilizers, even if they are being used for nonpsychiatric indications. Beta blockers for nonpsychiatric indications, except for propranolol, are permitted as described in Section 6.5.2.
- Other nonpsychopharmacologic drugs, substances, or herbal preparations with psychotropic effects

Within 14 Days Prior to Randomization:

- Anxiolytics (benzodiazepines and nonbenzodiazepines). If subjects are taking anxiolytics at Day −14, the dose should be tapered and stopped prior to Day −1 according to appropriate taper for benzodiazepines and clinical judgment.

Within 90 Days Prior to Randomization:

- Medications used to treat depression other than the ADT that is being utilized for the trial

Within 180 Days Prior to Randomization:

- Investigational drugs/procedures

At Any Time in the Past:

- ECT
- Neuro-modulation devices (transcranial magnetic stimulation, vagus nerve stimulation, or transcranial direct current stimulation, etc)

Use of a computer, web, or smartphone software-based application or equivalent for mental health or depression is prohibited during the trial.

Use of cannabis products is prohibited during the trial. Subjects reporting cannabis use or testing positive for cannabis may continue in the trial following medical monitor discussion and approval; however, subjects should be instructed not to use any cannabis

products during the trial as cannabis use may impact the potential efficacy of the digital intervention.

All treatments prohibited before screening or randomization are also prohibited during the trial.

6.5.2 Permitted Medications

One of the following will be required as background ADT (generic or branded is allowed):

Selective Serotonin Reuptake Inhibitors:

- Escitalopram (Lexapro®) tablets, 10 to 20 mg/day
- Citalopram (Celexa®) tablets, 20 to 40 mg/day
- Fluoxetine (Prozac®) capsules, 20 to 80 mg/day
- Paroxetine (Paxil CR®) controlled-release tablets, 25 to 62.5 mg/day
- Paroxetine (Paxil®) tablets, 20 to 50 mg/day
- Sertraline (Zoloft®) tablets, 50 to 200 mg/day

Serotonin-norepinephrine Reuptake Inhibitors:

- Duloxetine (Cymbalta®) delayed-release capsules, 60 to 120 mg/day
- Venlafaxine XR (Effexor XR®) extended-release capsules, 150 to 225 mg/day
- Venlafaxine ER extended-release tablets, 150 to 225 mg/day
- Desvenlafaxine (Pristiq®) extended-release tablets, 50 to 100 mg/day

Other:

- Bupropion XL (Wellbutrin®) extended-release tablets or Bupropion (Wellbutrin) tablets, 300 mg/day
- Bupropion SR (Wellbutrin) sustained-release tablets, 300 to 400 mg/day

The following are other permitted concomitant treatments for this trial:

- As-needed use of common cold preparations. Subjects should be instructed not to take cold preparations within 24 hours before a remote visit.
- Use of the sedative hypnotics zolpidem, zaleplon, or eszopiclone for sleep. The maximum dose should not exceed 10 mg/night for these medications (zolpidem extended-release: 12.5 mg/night), and use must not exceed 2 times per week. Subjects will be instructed not to take zolpidem, zaleplon, or eszopiclone within 24 hours before a remote visit or 8 hours prior to using the digital mobile application.

- Use of nonbenzodiazepine sleep aids such as melatonin or melatonin receptor agonists are permitted for sleep on an as needed basis, but should not be used 8 hours prior to using the digital mobile application.
- Trazadone may also be used for the management of sleep in doses up to 100 mg per night, but should not be used 8 hours prior to using the digital mobile application.
- Use of beta blockers for nonpsychiatric indications (eg, hypertension) are permitted following consultation and approval by the medical monitor. Subjects must be on a stable dose for a minimum of 30 days prior to baseline (Day 1), without any changes in dosing expected for the trial duration. Note: the use of propranolol, regardless of indication, is prohibited during trial participation and must be discontinued 7 days prior to randomization as described in Section 6.5.1.
- Other medications/treatments if not listed as prohibited in Section 6.5.1.

6.5.3 Rescue Medications

The subject's best medical interests should guide the investigator in the management of conditions that are pre-existing or that develop during the trial (intercurrent illness or AEs). For the AEs other than worsening of depressive symptoms, the investigator may initiate appropriate medications. If the subjects experience worsening of depression to such an extent that, in the investigator's opinion, the subject cannot continue in the trial, the subject will be discontinued and treated with appropriate medications as per the standard of care.

6.6 Intervention After the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, institutional review boards (IRBs) and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the trial site.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

A subject may remain in the trial, even if nonadherent with the treatment sessions during the treatment period; all trial procedures should still be performed, including the primary and secondary endpoints and documentation of AEs and pharmacologic or other treatments that may have occurred.

7.3.2 Treatment Discontinuation

After CT-152 or sham assignment, a subject may stop CT-152 or sham permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, require treatment with a prohibited medication or therapy, or other issues, as determined by the investigator.

When a subject discontinues or is withdrawn from the trial, the investigator will perform a final assessment, including the procedures indicated in the schedule of assessments (Table 1.3-1) for Day 42 as well as subject debriefing (subjects who discontinue early before Week 6) or Day 70 (subjects who discontinue early from the trial after Week 6). The Day 42 or Day 70 procedures should be performed on the last day the subject utilizes the double-blind digital mobile application or as soon as possible after the subject discontinues in order to complete all safety and effectiveness measurements.

In the event that a subject discontinues, every effort will be made by the investigator to determine why a subject fails to return for necessary visits or is dropped from the trial to record the reasons for withdrawal as thoroughly as possible. Reasonable efforts will be made by trial site staff to retain subjects in the trial and to complete remote visits and telephone contacts. Efforts will include outreach via telephone or e-mail when a subject misses a remote visit or telephone contact and rescheduling missed remote visits and telephone contacts within the ± 3 day visit window.

The digital mobile application on the discontinued subject's smartphone device will be uninstalled as described in Section 6.2.1.

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

A subject may temporarily interrupt or discontinue CT-152 or sham for the reasons listed below:

- Adverse event

  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing CT-152 or sham places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to CT-152 or sham)
    - Serious AE (SAE)
    - Other safety concerns or AEs
- Death
- Failure to meet randomization criteria
- Lack of efficacy
- Lost to follow-up
- Physician decision
- Protocol deviation
- Trial site terminated by sponsor
- Required treatment with prohibited medication or therapy
- Trial terminated by sponsor
- Technical problems
- Withdrawal by subject

If the subject temporarily interrupts or discontinues CT-152 or sham due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.4 must be followed.

7.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether remote visit or telephone contact).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).

- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt or discontinue CT-152 or sham, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.1 and Section 7.3.2, respectively). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should follow the procedures outlined in Section 7.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

Subjects who were randomly assigned and withdraw from the trial will not be replaced, regardless of the reason for withdrawal.

If the subject withdraws from the trial, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Day 70 (Week 10), who do not have a known reason for discontinuation (eg, withdrew consent or AE), will be classified as "lost to follow-up".

The trial site will make 3 documented attempts to contact the subject by telephone and in the event the trial site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

For lost to follow-up subjects, the digital mobile application on their smartphone device will be disabled.

If the subject was classified as “lost to follow-up”, “Were you able to contact the subject?”, “Date of contact/Date of final contact attempt” and “Contact method” will be recorded in eSource.

8 Trial Procedures

Subjects will participate in the trial for up to 13 weeks. This includes a screening period of up to 3 weeks; CCI [redacted] Extensions to the screening period, if requested by the investigator, may be granted after discussion and approval by the medical monitor.

The treatment period will be for 6 weeks (Day 1 [baseline] to Week 6) and subjects will have a remote visit at Weeks 2, 4, and 6 and will be contacted by telephone at Weeks 1, 3 and 5. Subjects will be required to be adherent with their digital mobile application exercises during the treatment period.

After Week 6, subjects will continue participation in the trial during the extension period (Weeks 7 to 10). In the extension period, the digital mobile applications will remain installed for each group. Subjects will continue to receive brief SMS messages reminding subjects of the previously completed CT-152 or sham treatment courses (see Section 6.1.1 for further details), and will continue their ADT. Subjects will have a remote visit at Weeks 8 and 10 and will be contacted by the trial site by telephone at Weeks 7 and 9.

The end of the trial will be Week 10.

All remote visits and telephone contacts after baseline will have a ± 3 day visit window to allow for variations in subject schedules and for weekends. Every effort should be made to have the remote visit or telephone contact on the designated trial day to ensure that the overall treatment period in the protocol has been maintained. Subsequent remote visits and telephone contacts should be based on the date of the baseline visit, not the previous remote visit/telephone contact. It is suggested that telephone contacts with the subject be scheduled in advance. If advanced scheduling is not possible, and the subject is not able to be reached by telephone on the first attempt, the trial site should make 3 more attempts to contact the subject, considering alternative days to reach the subject within the designated time frame.

The assessments to be conducted during the trial are summarized in the schedule of assessments (Table 1.3-1). A brief summary of the assessments to be performed at each visit is provided below.

The screening procedures and data collection may be performed remotely or in person, at the discretion of the investigator, and a minimum of 7 consecutive days will be required for screening. The following information will be collected during the screening period:

- Demographic information (collection date, age, sex, race, and ethnicity).
- Medical history of significance including relevant surgical procedures. A general clinical evaluation will be performed, including concurrent medical conditions, medical history over the past 2 years, and medical history beyond 2 years that is considered to be clinically relevant per the investigator's judgment.
- Prior and concomitant medication including confirmation of ADT use per the eligibility criteria. The dose and schedule of ADT, start/stop dates, as well as whether brand or generic medication is being taken will be recorded.
- Washout from prohibited concomitant medications, if applicable, will begin after consent has been obtained (see Section 6.5.1).
- Psychiatric history and diagnosis, including description of all prior treatments for psychiatric disorders, start date of current episode, and number of previous episodes. This includes the *DSM-5* diagnosis of MDD that will be made by an adequately trained and experienced clinician. The M.I.N.I will be used to confirm the subject's diagnosis of MDD and to rule out exclusionary comorbid psychiatric disorders. Detailed instructions for administration of this structured interview will be provided.
- The Antidepressant Treatment Response Questionnaire (ATRQ), used to collect a subject's history of pharmacologic treatment for their current episode, will be administered as part of the collection of a subject's psychiatric history and will be utilized to determine eligibility for entry into the trial.
- Substance usage history, current alcohol intake including amount and frequency, smoking status including history, and history of recreational drug use.
- The following will be administered by the trial site staff: HAM-D_{17} and C-SSRS.
- The following will be completed by the subject: PHQ-9 and CCI [redacted]
- The subjects will also perform a urine pregnancy test (females of childbearing potential) and a urine drugs-of-abuse test.
- The subject will download the digital mobile application onto their smartphone device.
- Prior/concomitant therapy and AEs will be recorded.

External quality oversight methods will be used by CCI to promote appropriate subject enrollment. Such methods will require trial sites to communicate certain aspects of subject data during the screening period to CCI, as detailed in the Site Operations Manual. An assessment on inclusion and exclusion criteria will be made to determine the subject's eligibility by the CCI. Subjects cannot be enrolled until trial site personnel have received the final CCI notification from the medical monitor or clinical scientist. The investigator is responsible for ensuring that subjects are eligible for enrollment into the trial and for assessing subject safety throughout the trial.

As a means of improving subject safety and data quality, verification of subject eligibility will be cross-checked against a centralized trial subject database to identify potential violations. Data relating to dual enrollment, washout period, prior screen fails, and dual screenings will be reported. Subjects will be asked to authorize that their unique subject IDs be entered into a registry with the intent of identifying subjects who may meet exclusion criteria for participation in another clinical trial.

The following will be performed at the remote baseline visit on Day 1:

- Confirmation of eligibility (including administration of the HAM-D_{17} by trial site staff).
- Check of ADT compliance.
- Randomization to 1 of 2 digital mobile applications (CT-152 or sham).
- The baseline MADRS must be completed prior to or on the day of the baseline visit, or prior to usage of the digital therapeutic treatment following randomization. The MADRS is conducted by the blinded and independent rater and should be scheduled by the trial site staff.
- The following will be administered by the trial site staff: CGI-S and C-SSRS.
- The following will be completed by the subject: GAD-7 and WHODAS 2.0.
- Prior/concomitant therapy and AEs will be recorded.

Treatment Period

The following will be performed during the remote visits at Weeks 2, 4, and 6:

- Check of ADT compliance.
- Adherence check of the use of the digital mobile application (Weeks 2 and 4 only).
- The MADRS will be conducted by the blinded and independent rater. Except for the baseline MADRS (see above), the MADRS at other visits may occur separately from the remote trial site visit but must be performed within the window.
- The following will be administered by the trial site staff: CGI-S and C-SSRS.

- The following will be completed by the subject: GAD-7, WHODAS 2.0 (Week 6 only), PHQ-9 (Weeks 4 and 6 only), CCI and CCI
- The principal investigator or the clinical trial member most familiar with the subject will complete the CCI
- Concomitant medications and AEs will be recorded.

During each telephone contact by the trial site at Weeks 1, 3 and 5, concomitant medications and AEs will be recorded and an adherence check of the use of the digital mobile application will be performed.

Extension Period

The following will be performed during the remote visits at Weeks 8 and 10:

- Check of ADT compliance.
- The MADRS will be conducted by the blinded and independent rater. The MADRS at Weeks 8 and 10 may occur separately from the remote trial site visit but must be performed within the window.
- The C-SSRS will be administered by trial site staff.
- The GAD-7 will be completed by the subject.
- Concomitant medications and AEs will be recorded.

During each telephone contact by the trial site at Weeks 7 and 9, concomitant medications and AEs will be recorded.

All MADRS assessments during the trial will be conducted by the blinded and independent rater, and will be recorded. Regular quality reviews of MADRS audio recordings will be performed in order to verify the quality of the MADRS interview and accuracy of scoring. The process for data oversight will be outlined in the Site Operations Manual.

At the conclusion of Week 10 or at early discontinuation early from the trial, a debriefing session will occur with the subject. Trial site staff will describe the components of each digital therapeutic and discuss the trial hypothesis, (ie, that one digital therapeutic was hypothesized to be more beneficial in improving depression symptoms based on a small study conducted previously). Trial site staff should explain that a trial (ie, the one in which they participated) was needed to further evaluate these initial findings. Subjects will be told the reason for the hypothesis blinding, ie, subjects would be less likely to question the efficacy of the treatment in which they were assigned. Adequate protective measures and resources will be available in the instance a subject is adversely affected by

the withheld information. Trial site staff will be provided with debriefing guidelines to assist in these discussions with the subjects.

All results from assessments should be recorded in eSource.

For this trial, only individuals who have been properly trained may administer the clinician-administered scales. Assessments for the M.I.N.I., HAM-D_{17}, C-SSRS, and CGI-S will be administered by the trial sites using the provided scales. Training on the administration of these assessments will be conducted.

No ratings as part of trial assessments may be performed by a rater prior to approval by sponsor and completion of rater training/certification. It is preferred that as often as possible, for each subject, the site-administered scales be performed by the same person throughout the trial.

The GAD-7, PHQ-9, WHODAS 2.0, CCI will be completed by the subject electronically. The subjects will be encouraged to complete the assessments prior to but within the window of the scheduled remote visit. All subject self-assessments should be reviewed and verified by the trial site for completeness during the remote visit, or within the window of the remote visit.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The trial team will be informed of these incidents in a timely fashion.

8.1 Efficacy Assessments

8.1.1 Montgomery-Asberg Depression Rating Scale

The MADRS will be administered by a blinded and independent rater at the time points described in the schedule of assessments (Table 1.3-1). The baseline MADRS must be completed prior to or on the day of the baseline visit, or prior to usage of the digital therapeutic treatment following randomization. The MADRS at other visits may occur separately from the remote trial site visit but must be performed within the window.

The MADRS raters are selected, assigned, and managed by a central vendor separate from the trial sites.

The MADRS is the primary efficacy assessment of the subject's level of depression and must be administered utilizing the Structured Interview Guide for the MADRS (SIGMA). The MADRS consists of 10 items, each rated from 0 to 6. A higher score on the MADRS represents a higher severity of the level of depression.

8.1.2 Generalized Anxiety Disorder-7

The GAD-7 will be self-reported by the subject electronically within the window of the remote visits described in the schedule of assessments (Table 1.3-1). It is recommended that the GAD-7 be completed prior to the remote visit.

The GAD-7 is designed to assess anxiety in subjects. The scale contains 7 items and each item is rated from 0 (not at all) to 3 (nearly every day). The score ranges from 0 to 21. A higher score on the GAD-7 represents greater anxiety symptomatology.

8.1.3 Clinical Global Impressions-Severity

The CGI-S will be administered by trial site staff at the time points described in the schedule of assessments (Table 1.3-1).

The CGI-S is a standardized, clinician-administered global rating scale that measures disease severity on a 7-point Likert scale. A higher score on the CGI-S represents a higher severity of disease.

8.1.4 Patient Health Questionnaire-9

The PHQ-9 will be self-reported by the subject electronically within the window of the visits at the time points described in the schedule of assessments (Table 1.3-1). It is recommended that the PHQ-9 be completed prior to the visit.

The PHQ-9 is a standardized, self-administered rating scale that assesses the severity of depressive symptoms. The scale consists of 9 items, representing the 9 criteria upon which the diagnosis of DSM-IV depressive disorders is based. A higher score on the PHQ-9 represents a higher severity of depressive symptoms.

8.1.5 World Health Organization Disability Assessment Schedule 2.0

The WHODAS 2.0 will be self-reported by the subject electronically within the window of the remote visits at the time points described in the schedule of assessments (Table 1.3-1). It is recommended that the WHODAS 2.0 be completed prior to the remote visit.

The WHODAS 2.0 is a 36-item self-assessment scale to measure a subject's function and disability across 6 domains of life: cognition (understanding and communicating), mobility (moving and getting around), self-care (hygiene, dressing, eating, staying alone),

getting along (interacting with others), life activities (domestic responsibilities, leisure, work and school), and participation (community and society).

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[redacted]

8.2 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.3.

8.2.1 Clinical Laboratory Assessments

A urine drugs-of-abuse screen and pregnancy testing will be performed as described in Section 8.4.7 and Section 10.3, respectively.

Other clinical laboratory testing is not planned, but the investigator may perform tests as needed to ensure subject safety. The medical monitor should be consulted prior to clinical laboratory testing.

8.2.2 Suicidality Monitoring

Suicidality monitoring will occur at the time points described in the schedule of assessments (Table 1.3-1).

In the event of clinically important treatment emergent suicidal ideation or suicidal behavior, as per the investigator's judgment, the subject may be withdrawn from the trial and may receive appropriate medical care, which may include increasing the dose of ADT or using other medications as per the standard of care treatment for depression and/or access to a suicide hotline. The investigator will follow-up until the subject's condition has stabilized.

Clinically important suicidality may include but is not limited to:

- Suicidal behavior (with or without intent of suicide or serious self-harm).
- Acute suicidality to such a degree that precaution against suicide must be exercised.
- Response of "yes" to C-SSRS ideation items 4 or 5 or any of the C-SSRS behavioral items.
- Score of "4", "5", or "6" on the MADRS suicidal thoughts item.

8.2.2.1 Columbia-Suicide Severity Rating Scale

The C-SSRS will be administered by trial site staff at the time points described in the schedule of assessments (Table 1.3-1).

The C-SSRS is an assessment tool that evaluates suicidal ideation and behavior. The "Baseline/Screening" Version will be used for the first administration (at the screening visit). This version will evaluate a lifetime assessment of suicidal ideations and behaviors, as well a past 12-month evaluation of suicidal ideations and a past 24-month evaluation of suicidal behaviors. Subsequent visits will utilize the "Since Last Visit" Version.

8.3 Adverse Events

8.3.1 Definitions

Note: The below definitions of AE, SAE, device-related AE, and unanticipated adverse device effect (UADE) are based on ISO14155 and 21 CFR 812 (and related US Food and Drug Administration [FDA] medical device clinical trial guidance documents).

Adverse event: Any untoward medical occurrence, unintended disease or injury, or untoward clinical sign in subjects, whether or not related to the digital therapeutic. Including any newly occurring event or previous condition that increases in severity or frequency following enrollment in the trial.

Note: Adverse events would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred.

Serious AE: An AE where the outcome is one of the following:

a) Led to death
b) Led to a serious deterioration in the health of the subject, that either resulted in
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function, or
    3) In-patient hospitalization or prolongation of existing hospitalization, or

4) A medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to body structure or a body function.

c) Led to fetal distress, fetal death, or a congenital abnormality

d) Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, worsening of depression or anxiety symptoms; disease progression; suicidality (ideation); develop or resume drug dependency or drug abuse.

Note:

- Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
- Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
- Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.

Device-related AE: Events directly attributable to the device itself.

Unanticipated adverse device effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Nonserious AEs: All AEs that do not meet the criteria for a "serious" AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in the eSource. The severity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

Causality: Assessment of causal relationship of an AE to the use of CT-152 is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between CT-152 and the AE.
Not Related:	There is no temporal or causal relationship between CT-152 and the AE.

Additional definitions (based on Otsuka internal procedures):

Treatment-emergent AEs (TEAEs): TEAEs are defined as an AE that began after at least one occurrence of CT-152 or sham; or if the event was continuous from baseline and was worsening, serious, related, or resulted in death, discontinuation, or interruption of investigational product.

8.3.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents provided by the sponsor and in eSource. Adverse event collection will begin after a subject signs the ICF through the last visit or contact.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

A reported AE that undergoes a change in severity, seriousness, or toxicity should be reported as a new AE on the source documents and on the eSource provided by the sponsor.

Adverse event, start date, end date, seriousness, severity, relationship to trial treatment (causality), action taken with trial treatment and outcome will be recorded on the source documents and in eSource.

8.3.2.1 Anticipated Adverse Events

Adverse events related to mobile device use may include dizziness, fatigue, or headache. No attributable AEs to CT-152 were observed in previous research studying CT-152. Please refer to the CT-152 Investigator Brochure for additional risk information.

Subjects enrolling in this trial will have a diagnosis of MDD per *DSM-5* criteria. Any worsening of the symptoms associated with MDD, as well as other relevant comorbidities for this population including anxiety disorder or new or relapse to substance use are anticipated AEs for this population.

Efficacy assessments and safety variables per Section 8.1 and Section 8.2 captures measurement criteria for some of these anticipated AEs. Subjects are under the care of qualified HCPs during the trial, and will be assessed for all AEs (anticipated as noted here) and unanticipated.

The risk profile of ADTs used as standard of care in clinical practice is well understood and is detailed in the package insert of the medications. Based on the known risk profile of the ADT medications and preliminary risk assessment of CT-152, the sponsor believes, that there is no additional risks to the subjects.

8.3.2.2 Device Malfunction

For the purposes of this trial, it is expected that device malfunctions will be observed by either the investigator or subject. In both cases, these will be reported to the call center and processed as described in Section 6.2.2 for PQCs and product nonconformances.

8.3.2.3 Unanticipated Adverse Device Effects

An unanticipated device adverse effect includes any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence. Any unanticipated device adverse effect must be reported by fax or e-mail to the sponsor or designee using the contact information on the cover page of this protocol as soon as the trial site personnel are made aware of an event (within 24 hours). The sponsor will review all malfunctions and determine if they are unanticipated adverse device effects, and report to regulatory or other bodies (as appropriate).

8.3.2.4 Immediately Reportable Events

Immediately Reportable Event:

- Any SAE (Note: all SAEs whether anticipated or not must be reported to the sponsor or sponsor's designee as immediately reportable events [IREs])
- Pregnancies are also defined as IREs. If the subject becomes pregnant during the trial, the subject should be discontinued. Pregnancy will only be documented on the AE eSource if there is an abnormality or complication. This does not include pregnancy of the partner of the subject.
- Any UADE

The investigator must immediately report (within 24 hours), using an IRE form, after the investigator or site personnel become aware of any IRE (SAE, confirmed pregnancy, or UADE), by fax or e-mail to the sponsor or designee using the contact information on the cover page of this protocol (Please note that the IRE form is NOT the AE eSource.).

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate

supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

8.3.3 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/clinical research organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of CT-152 or sham will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Global Pharmacovigilance Department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with CT-152 or sham.

8.3.4 Follow-up of Adverse Events

8.3.4.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eSource with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

8.3.4.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 28 calendar days after the last subject visit or contact.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eSource and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to the last remote visit or telephone contact for the entire trial), this

must be reported to the sponsor and recorded in the AE eSource and the IRE form, according to the appropriate reporting procedures described in Section 8.3.2.4.

It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor. The investigator will follow IREs until the events are:

- resolved,
- stabilized,
- the subject is lost to follow-up, or
- has died.

Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for subjects that become pregnant.

8.3.4.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of CT-152 or sham, should be reported to the sponsor according to the procedures outlined in Section 8.3.2.4. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.4 Other Assessments

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8.4.3 Mini International Neuropsychiatric Interview

The M.I.N.I. (Version 7.0.2 for *DSM-5*) will be used as a tool for conducting a structured interview for eligibility assessment at the screening visit (Table 1.3-1).

The M.I.N.I. is a widely used structured diagnostic interview instrument developed for *DSM-5* psychiatric disorders. A qualified rater will conduct the interview.

The results of the M.I.N.I. will be compared with the inclusion/exclusion criteria for evaluation of comorbid diagnoses.

8.4.4 Antidepressant Treatment Response Questionnaire

The MGH-ATRQ will be used to collect a subject's history of pharmacological treatment for their current episode. It will be administered at screening as part of the collection of the subject's psychiatric history and will be utilized to determine eligibility for entry into the trial.

8.4.5 Hamilton Rating Scale for Depression, 17-Item

The HAM-D_{17} will be administered by trial site staff at the time points described in the schedule of assessments (Table 1.3-1) as part of the eligibility assessments.

The HAM-D_{17} will be administered utilizing the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D). Detailed instructions for administration of this structured interview will be provided.

8.4.6 Diagnostic Criteria for Major Depressive Disorder

The subject's *DSM-5* diagnosis of MDD, based on the clinical interview and medical/psychiatric history and confirmed by the M.I.N.I., should be documented in eSource.

8.4.7 Urine Drugs-of-Abuse Screen

Urine drugs-of-abuse screens will be performed by the subject after signing the informed consent and before the baseline visit on Day 1. Additional tests may be required for further evaluation at unscheduled time points as warranted by investigator judgment.

If the screening visit is performed in person, the urine drugs-of-abuse screen will be performed at the trial site.

If the screening visit is performed remotely, urine drug screen test kits and instructions will be provided to the trial sites to ship to the subject after the informed consent is signed. The subject is to perform the test and provide evidence of the test result to the trial site staff. Details can be found in the Site Operations Manual.

Alternative methods of test performance/acquisition may be able to be accommodated following discussion with medical monitor.

Subjects with a positive urine drug screen resulting from use of cannabis, or prescription or over-the-counter medications, or products that, in the investigator's documented opinion, do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor. However, subjects will be instructed not to use cannabis products during the trial as per Section 6.5.1, as it may impact the potential efficacy of the digital intervention. The investigator may retest a subject if it is believed a positive urine drug screen is a false positive test, following discussion with the medical monitor.

See Section 10.2 for the list of drugs-of-abuse that will be tested for.

8.4.8 Pregnancy Test

Females of childbearing potential will perform a urine pregnancy test after signing the informed consent and before the baseline visit on Day 1.

If the screening visit is performed in person, the urine pregnancy test will be performed at the trial site.

If the screening visit is performed remotely, urine pregnancy test kits and instructions will be provided to the trial sites to ship to the subject after informed consent is signed. The subject is to perform the test and provide evidence of the test result to the trial site staff. If the test result is positive, the subject is to repeat the test in 2 days (> 48 hours from first test) and provide evidence of the repeat test result to the trial site staff. Details can be found in the Site Operations Manual.

Alternative methods of test performance/acquisition may be able to be accommodated following discussion with the medical monitor.

A confirmed positive pregnancy test result after signing the informed consent and before the baseline visit on Day 1, will require exclusion of the subject. A positive pregnancy test after the baseline visit will require discontinuation of the subject from the trial.

See Section 10.3 for contraceptive guidelines and collection of pregnancy information.

9 Statistical Considerations

9.1 Sample Size

The initial sample size is calculated to detect a 3-unit difference between CT-152+ADT and sham+ADT in the change from baseline in MADRS total score with 85% power at a 2-sided $\alpha = 0.05$ level, assuming a common standard deviation of 9. The resulting sample size is 324 evaluable subjects in total (162 subjects in each arm). To compensate for subjects that fail to have evaluable assessments of MADRS total score in the full analysis set (FAS) sample (estimated at up to 10% of all subjects), a total of 360 subjects (180 subjects in each arm) will be randomized in this trial.

Due to the limitations of applying assumptions on the treatment effect size, and in order to ensure adequate power of the trial, an unblinded interim analysis will be conducted by a Data Monitoring Committee (DMC; see Section 9.5.1). The final sample size could be increased to 540 subjects (270 subjects in each arm) as per recommendation of the DMC. Using the O'Brien-Fleming spending function[49] a significance level of 0.003 (2-sided) is allocated to this interim analysis. The corresponding final significance level is 0.049 (2-sided).

The trial will randomize eligible subjects 1:1 across approximately 50 trial sites. The sample size at any single trial site will be capped at approximately 15% of the total number of randomized subjects. Randomization will be stratified by trial site.

9.2 Datasets for Analysis

The following analysis datasets are defined for this trial:

- Enrolled sample – all subjects enrolled in the trial.
- Randomized sample – all subjects allocated based on the randomization process and recorded in the database. Subjects treated without being randomized will not be considered as randomized and therefore will not be included in any efficacy or safety population analyses.

- Safety sample – all randomized subjects who receive at least 1 occurrence of either CT-152 or sham use. All safety assessments will be performed on the safety analysis set. If any subjects receive a treatment that differs from the assigned treatment, then the safety analyses will be conducted on the treatment actually received.
- FAS sample – all randomized subjects who receive at least 1 occurrence of either CT-152 or sham use, and have baseline and at least 1 postbaseline assessment of MADRS total score. Subjects included in the FAS sample are defined as evaluable subjects.
- Per-protocol (PP) analysis sample – all subjects in the FAS Sample who were treated for 6 weeks, did not have a major protocol deviation, and were adherent to CT-152 or sham treatment in this trial. The classification of protocol deviations will be established in a blinded review by the sponsor in a meeting prior to breaking the blind. The PP analysis set will only be used for sensitivity analysis of the primary efficacy and key secondary variables.

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

When the possibility of "missing not at random" cannot be ruled out, a selection model, pattern-mixture model, and other models will be used to explore the impact of missing data and potential mechanisms of "missing not at random" and investigate the response profile of dropout reasons. See Section 9.4.1.5 for more details.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Endpoint Analysis

The null hypothesis of the statistical test comparing CT-152+ADT and sham+ADT, based on the primary efficacy endpoint, is that the change in MADRS using CT-152+ADT is equal to the change in MADRS using the sham+ADT.

$$H_0: \Delta\mu_{\text{MADRS CT-152+ADT}} = \Delta\mu_{\text{MADRS sham+ADT}}$$

$$H_A: \Delta\mu_{\text{MADRS CT-152+ADT}} \neq \Delta\mu_{\text{MADRS sham+ADT}}$$

The primary analysis will be conducted on the change from baseline in MADRS total score to the final on-therapy evaluation (Week 6) based on the FAS Sample adjusted for the baseline MADRS total score.

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9.4.1.1.1 Primary Estimand

The primary estimand defining the treatment effect of interest in the protocol uses the hypothetical strategy specified in the International Council for Harmonisation (ICH) E9 Addendum. The objective of the primary analysis is to compare the efficacy of CT-152 and sham. The estimand, or target of estimation, following the hypothetical strategy is the treatment effect seen, had no withdrawals occurred. Subjects who withdraw from a CT-152 or sham either could have lost their treatment effect, had the subjects not taken any other treatment after withdrawal, or could have their treatment effect been masked, had the subjects taken other treatment after withdrawal. This means that any observations taken after subjects stop CT-152 or sham will most likely not contribute relevant information about the treatment effect. Due to this strategy, the last collected efficacy assessment after premature trial discontinuation will be done only once at the early termination (ET) visit. Every effort will be made to complete all of the ET evaluations prior to administering any other treatment. In the case of terminal or lost to follow-up events no ET evaluations would be expected, and only scheduled assessments performed before such an event has occurred.

The primary estimand for this trial is defined by the following components:

- Target population: FAS Sample
- Endpoint: change from baseline to Week 6 in the MADRS total score
- Intercurrent events: premature treatment discontinuation
- Measure of intervention effect: difference in endpoint means between CT-152+ADT and sham+ADT

In this hypothetical strategy, the event of withdrawing CT-152+ADT or sham+ADT is considered missing at random (MAR), and the primary endpoint of the trial could be considered as a combination of the measurements of on-treatment completers at Week 6 and the imputation of the endpoint to Week 6 following the trend in each treatment group using the mixed model repeated measurements (MMRM) method to impute missing data for subjects who withdraw CT-152+ADT or sham+ADT during the trial. All data collected during the trial treatment period will be used for statistical analysis. For the primary efficacy analysis, the treatment effect will be estimated using the MMRM method described in Section 9.4.1.1.2. Under the MAR assumption, MMRM provides an unbiased estimate of treatment effect for the treatment period. Analyses with missing values imputed by multiple imputation under missing not at random (MNAR), and other methods will be performed as sensitivity analyses.

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9.4.1.1.2 Primary Analysis Method

The primary analysis will utilize a MMRM with treatment, visit, treatment by visit interaction, and site as fixed effects to assess heterogeneity of treatment effects. This model will also include an interaction term of visit by baseline MADRS total score as a covariate. Observed data from all planned visits during the 6-week treatment period will be included in the model. An unstructured covariance matrix will be used to model the within subject variance. The primary comparison between the CT-152+ADT or sham+ADT at Week 6 will be estimated as the difference between least squares means utilizing the computing software SAS procedure PROC MIXED.

The mathematical formula for the MMRM model is as follows:

$$\boldsymbol{y} = \boldsymbol{X}\beta + Zu + \epsilon$$

Where

$\boldsymbol{y}$ denotes the observed vector of change from baseline to Week 6 in MADRS total score;

$\boldsymbol{X}$ is the known matrix for the fixed effects and covariate;

β is an unknown fixed-effect parameter vector;

Z is the known matrix for the random effect of subject;

u is an unknown vector of random effect of subject with mean **0** and variance-covariance matrix **G** (unstructured covariance matrix);

ϵ is an unknown vector of random errors with mean **0** and variance **R.**

In case there is a convergence problem with the MMRM model with the unstructured variance-covariance matrix, the following structures other than unstructured will be used in order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry. The first (co)variance structure converging to the best fit will be used as the primary analysis. If a structured covariance has to be used, the "sandwich" estimator of the standard error of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix.

Small trial sites will be defined as trial sites that do not have at least one evaluable subject (evaluable with regard to the primary efficacy variable) in each treatment arm. All small trial sites will be pooled to form "pseudo sites" for the purpose of analysis according to the following algorithm. Small trial sites will be ordered from the largest to the smallest based on the number of evaluable subjects (ie, subjects who have baseline and at least one postbaseline value for the primary endpoint in the treatment period).

The process will start by pooling the largest of the small trial sites with the smallest of the small trial sites until a nonsmall trial sites is formed. This process will be repeated using the trial sites left out of the previous pass. In case of ties in trial sites size, the trial site with the smallest trial site code will be selected. If any trial sites are left out at the end of this process, they will be pooled with the smallest pseudo trial sites, or if no pseudo trial sites exist, they will be pooled with the smallest nonsmall trial site.

9.4.1.2 Analyses on Key Secondary Efficacy Endpoint and Other/Additional Efficacy Endpoints

The key secondary efficacy endpoint and other/additional efficacy endpoints will be analyzed based on the FAS as described for the primary analysis.

To control the overall type I error, the statistical tests based on the primary efficacy endpoint and the key secondary efficacy endpoint will be done using a hierarchical approach. The primary hypothesis will be tested at the 0.049 level and if successful in rejecting the null hypothesis stated above, analysis of the key secondary endpoint will be tested at the type I error level of 0.049.

Should the primary outcome not achieve statistical significance, the key secondary endpoint will be examined as an other efficacy endpoint.

9.4.1.2.1 Key Secondary Efficacy Endpoint Analysis

Change from baseline to Week 6 in the GAD-7 total score will be analyzed using the same method (MMRM) as in the primary analysis with a replacement of the interaction term of visit by baseline GAD-7 total score as a covariate. The null hypothesis of the statistical test comparing CT-152+ADT and sham+ADT, based on the key secondary efficacy endpoint, is that the change from baseline to Week 6 in the GAD-7 total score using CT-152+ADT is equal to the change from baseline to Week 6 in the GAD-7 total score using sham+ADT.

$$H_0: \Delta\mu_{\text{GAD-7 CT-152+ADT}} = \Delta\mu_{\text{GAD-7 sham+ADT}}$$

$$H_A: \Delta\mu_{\text{GAD-7 CT-152+ADT}} \neq \Delta\mu_{\text{GAD-7 sham+ADT}}$$

where $\Delta\mu_{\text{GAD-7 CT-152+ADT}}$ and $\Delta\mu_{\text{GAD-7 sham+ADT}}$ are the change from baseline to Week 6 in the GAD-7 total score in CT-152+ADT and sham+ADT treatment groups, separately.

9.4.1.2.2 Efficacy Endpoints for Assessment of Durability

The durability of effect of CT-152 will be assessed based on MADRS total score and GAD-7 total score.

It will include 3 MADRS assessments at Weeks 6, 8, and 10. In addition to demonstrating an MCID group difference of 1.6 to 1.9 at Week 6 with statistical significance, durability will be demonstrated by a point estimate of the difference in change from baseline at Weeks 8 and 10 above 1.6, when comparing CT-152 and sham. Such point estimates will be provided using the same MMRM model in the primary efficacy analysis with change from baseline in MADRS total score at Week 8 and 10 as the dependent variable.

Durability based on GAD-7 will also include 3 assessments, at Weeks 6, 8, and 10, demonstrating a numerically larger improvement on point estimate of the difference in change from baseline in GAD-7 total score at Weeks 8 and 10 in CT-152 compared to sham. Such point estimates will be provided using the same MMRM model in the key secondary efficacy analysis with change from baseline in GAD total score at Week 8 and 10 as the dependent variable.

9.4.1.2.3 Other Efficacy Endpoints Analyses

Change from baseline to Weeks 2 and 4, separately, in the MADRS total score will be analyzed using the same MMRM model in the primary efficacy analysis.

Change from baseline to Weeks 2 and 4, separately, in the GAD-7 total score will be analyzed using the same MMRM model in the key secondary efficacy analysis.

Response on the MADRS is defined as a decrease of 50% or more on the MADRS total score from baseline. Response rates at Weeks 2, 4, and 6, separately, will be analyzed using the Cochran-Mantel-Haenszel General Association Test controlling, in last observation carried forward (LOCF) analyses, for trial site.

$H_0: \pi_{\text{CT-152+ADT}} = \pi_{\text{sham+ADT}}$

$H_A: \pi_{\text{CT-152+ADT}} \neq \pi_{\text{sham+ADT}}$

Where $\pi_{\text{CT-152+ADT}}$ and π_{sham} are the proportion of MADRS response rates at Weeks 2, 4, and 6 in CT-152+ADT and sham+ADT treatment groups, separately.

Change from baseline to Weeks 2, 4, and 6, separately, in CGI-S score will be analyzed using the same method as in the primary analysis with a replacement of the interaction term of visit by baseline CGI-S score as a covariate. The hypothesis tested is the null hypothesis that the change from baseline to each schedule week (Weeks 2, 4, and 6) in the CGI-S score using CT-152+ADT is equal to the change from baseline to each schedule week (Weeks 2, 4, and 6) in the CGI-S score using the sham+ADT.

$H_0: \Delta\mu_{\text{CGI-S CT-152+ADT}} = \Delta\mu_{\text{CGI-S sham+ADT}}$

$H_A: \Delta\mu_{\text{CGI-S CT-152+ADT}} \neq \Delta\mu_{\text{CGI-S sham+ADT}}$

Where $\Delta\mu_{\text{CGI-S CT-152+ADT}}$ and $\Delta\mu_{\text{CGI-S sham+ADT}}$ are the changes from baseline to Weeks 2, 4, and 6 in CGI-S score in CT-152+ADT and sham+ADT treatment groups, separately.

Change from baseline to Week 6 in the WHODAS 2.0 total score will be evaluated using the analysis of covariance with baseline as a covariate and treatment and, in LOCF analyses, trial site as main effects. The hypothesis tested is the null hypothesis that the change from baseline to Week 6 in the WHODAS 2.0 total score using CT-152+ADT is equal to the change from baseline to Week 6 in the WHODAS 2.0 total score using the sham+ADT.

$$H_0: \Delta\mu_{\text{WHODAS 2.0 CT-152+ADT}} = \Delta\mu_{\text{WHODAS 2.0 sham+ADT}}$$

$$H_A: \Delta\mu_{\text{WHODAS 2.0 CT-152+ADT}} \neq \Delta\mu_{\text{WHODAS 2.0 sham+ADT}}$$

Where $\Delta\mu_{\text{WHODAS 2.0 CT-152+ADT}}$ and $\Delta\mu_{\text{WHODAS 2.0 sham+ADT}}$ are the changes from baseline in Week 6 on the WHODAS 2.0 total score in CT-152+ADT and sham+ADT treatment groups, separately.

Change from screening to Weeks 4 and 6, separately, on the PHQ-9 total score will be analyzed using the same method as in the primary analysis with a replacement of the interaction term of visit by screening PHQ-9 total score as a covariate. The hypothesis tested is the null hypothesis that the change from screening to each schedule week (Weeks 4 and 6) in the PHQ-9 total score using CT-152+ADT is equal to the change from screening to each schedule week (Weeks 4 and 6) in the PHQ-9 total score using the sham+ADT.

$$H_0: \Delta\mu_{\text{PHQ-9 CT-152+ADT}} = \Delta\mu_{\text{PHQ-9 sham+ADT}}$$

$$H_A: \Delta\mu_{\text{PHQ-9 CT-152+ADT}} \neq \Delta\mu_{\text{PHQ-9 sham+ADT}}$$

Where $\Delta\mu_{\text{PHQ-9 CT-152+ADT}}$ and $\Delta\mu_{\text{PHQ-9 sham+ADT}}$ are the changes from screening to Weeks 4 and 6 in PHQ-9 total score in CT-152+ADT and sham+ADT treatment groups, separately.

Partial response on the MADRS is defined as ≥ 30% and < 50% reduction in MADRS total score from baseline. Partial response rates at Weeks 2, 4, and 6, separately, will be analyzed using the same statistical model for MADRS response.

$$H_0: \pi_{\text{CT-152+ADT}} = \pi_{\text{sham+ADT}}$$

$$H_A: \pi_{\text{CT-152+ADT}} \neq \pi_{\text{sham+ADT}}$$

Where $\pi_{CT\text{-}152+ADT}$ and $\pi_{sham+ADT}$ are the MADRS partial response rates at Weeks 2, 4, and 6 in CT-152+ADT and sham+ADT treatment groups, separately.

Response on the MADRS during the extension period is defined as full or partial, defined as ≥ 30% reduction in MADRS total score from baseline. Response rates at Weeks 8 and 10, separately, will be analyzed using summary statistics in LOCF analysis.

9.4.1.3 Control of Experiment-wise Type 1 Error

To control experiment-wise type I error, a hierarchical approach on the primary and key secondary efficacy endpoints will be applied as described in Section 9.4.1.2.

9.4.1.5 Sensitivity Analyses

Per-protocol analyses will be conducted as sensitivity analyses to the primary analysis, on the PP analysis set.

The MMRM model used for the primary efficacy endpoint assumes data are MAR, which is a reasonable assumption in longitudinal clinical trials in MDD.[52] However, the possibility of "missing not at random" (MNAR) data can never be ruled out. As sensitivity analyses, selection model[53] pattern-mixture model[54,55,56,57] and shared parameter model[58] will all be used to explore data missing mechanisms of MNAR and investigate the response profile of dropout reason. Adding a site by treatment interaction term into the MMRM model will assess heterogeneity of the treatment effects.

Subgroup analysis will be performed on gender, race, age group, and by cannabis use at screening (Yes/No). CCI

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9.4.2 Safety Analysis

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized by treatment group:

- TEAEs
- TEAEs potentially causally related to CT-152 or sham
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation from the trial

9.4.2.2 Clinical Laboratory Data

Urine drugs-of-abuse screen and pregnancy test results will be listed by subject.

9.4.2.3 Other Safety Data

Rates of the incidence of worsening depressive symptoms during the treatment period (depressive symptom severity entering the “severe” range: CGI-S increase of 2 or more points from baseline, or as judged by investigator evaluation) and the incidence of emergent clinically important suicidality (as described in Section 8.2.2) will be compared between CT-152 and sham groups in the safety analysis sets. Rates and their 95% confidence intervals will be reported and the estimated differences between groups will be provided.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Baseline and demographic characteristics including age, sex, race, and ethnicity will be summarized using descriptive statistics.

CCI [redacted]

9.5 Interim Analysis and Adaptive Design

An unblinded interim analysis of efficacy data will be conducted on approximately the first 180 randomized subjects. The unblinded interim analysis will be carried out when

these subjects have either completed the Week 6 visit or discontinued prior to Week 6. The difference between CT-152 and sham based on the primary efficacy endpoint will be tested at the unblinded interim analysis. To protect the overall type I error at the 2-sided alpha level of 0.05 (2-sided) and to limit the estimation bias, the following will be completed:

- A significance level of 0.003 (2-sided) will be allocated to this unblinded interim analysis. The corresponding final significance level is 0.049 (2-sided).
- The DMC will be allowed to make recommendations based on 1 of the 4 outcomes:
  - Early stop for efficacy if the unblinded interim analysis p-value is < 0.003 (2-sided; Early Efficacy), and all point estimates of difference in change from baseline to Weeks 6, 8, and 10 in MADRS total score CCI
  - Proceed as planned to 360 randomized subjects if the conditional power observed at the unblinded interim analysis is ≥ 85%; or is > 15% and ≤ 50% (Favorable or Unfavorable Zone).
  - Increase sample size from 360 randomized subjects to 540 randomized subjects, if the conditional power observed at the unblinded interim analysis is > 50% but < 85% (Promising Zone).
  - Early stop for futility if the conditional power observed at the unblinded interim analysis is ≤ 15% (Futility).

The sample size will be re-estimated only based on the conditional power determined at the interim analysis. The adaptive designs methodology published by Chen, DeMets, and Lan (2004)[59] will be used to increase the sample size based on an interim estimate of the treatment effect size, possibly combined with other external information, without inflating the type I error.

All the detailed calculations and re-estimation methods will be prespecified and included in the statistical analysis plan, interim analysis plan, and the DMC charter.

9.5.1 Data Monitoring Committee

A DMC will be chartered for this trial. The DMC will include at least 3 members, one of whom will be an expert in biostatistics for clinical trials, and at least one of which will have expertise in MDD treatment trials. The DMC will be convened at intervals described in the DMC charter to review data on recruitment, retention, interim analysis, and safety (including evaluation of discontinuation criteria), and to review data for completeness and quality during the trial. Discontinuation criteria will be prespecified and included in the DMC charter.

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10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations ICH GCP guidance international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific and medical appropriateness of the trial. Further, when working with eSource, the investigator, subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

10.1.2 Informed Consent

If the screening visit is performed in person, the informed consent process will be performed at the trial site.

If the screening visit is performed remotely, the informed consent process will be performed remotely.

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH GCP: Consolidated Guideline E6 and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB.

This trial will utilize an electronic informed consent form (eICF). The eICF utilizes the IRB-approved trial site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a trial subject as well as required trial procedures. Trial sites will have subjects review and sign the eICF prior to starting any trial procedures.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and

documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Prospective trial subjects will be provided with controlled access to the eICF application by trial site staff. When the trial site staff and the subject agree that the subject has enough information to make an informed decision to participate, the subject will electronically sign in the eICF application and an electronic date and timestamp will be applied to the signature. The subject will be provided a signed copy of the ICF. Any other parties required by the IRB (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the eICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation.

All subjects who have consented to participate in the trial will be given the opportunity to provide consent for tokenization. Participation in the tokenization is optional and a separate and similar consent process will be followed for the tokenization. Tokenization is further described in Section 10.4.

10.1.3 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. CT-152, sham, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject ID in eSource. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

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10.1.4 Quality Control and Quality Assurance

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH GCP: Consolidated Guideline (E6), and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit or conduct video conferencing with the trial sites during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.4.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, presence of required documents, the informed consent process, and a review of the eSource with source documents, as applicable. The investigator agrees to participate with audits.

Regulatory authorities may inspect the trial sites during or after the trial. The investigators will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in eSource along with the start date and details of the deviation.

10.1.6 Records Management

10.1.6.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical

records, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

Source documents and source data will be captured electronically (where permitted by local regulation) in this trial and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected into a system that is fully validated according to 21 Code of Federal Regulations Part 11. Changes to the data will be captured by an automatic audit trail.

Designated trial site staff will not be given access to the electronic source system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application, rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified per the monitoring plan and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator or their designee.

Remote monitoring of the original electronic source records will take place; however, on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to

ensure protocol adherence, to assess trial site operational capabilities and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

10.1.6.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP: Consolidated Guideline (E6) and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

Food and Drug Administration regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years after the date on which a New Drug Application is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified time frame. Notice of such transfer will be given to the sponsor in writing.

10.1.6.5 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if all of the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial subjects who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial subjects consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Urine Drugs-of-Abuse Screen

The urine drugs-of-abuse screen will test for the following:

- Methamphetamines
- Cocaine
- Benzodiazepines
- Oxycodone
- Morphine
- Tetrahydrocannabinol
- Phencyclidine
- Adulteration detection for oxidants, creatinine, pH, specific gravity, nitrites, and glutaraldehyde

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

There is no contraceptive guidance for this trial.

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy during the trial and for up to 28 calendar days after the last remote visit or contact, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 4: Tokenization

Linking subject data collected during a clinical trial to subject data collected outside of the trial (eg, real-world data [RWD] such as health insurance claims, electronic medical records, laboratory data from outside the trial, etc), can be beneficial to better understand a clinical intervention, efficiently conduct long-term analyses of effects of interventions beyond the duration of the clinical trial, improve clinical operations, etc. The sponsor is seeking to link clinical trial data and RWD to attain these goals. However, subject IDs are unique and internal to each trial and do not provide a way to link subjects across RWD datasets. To better understand the long-term effects of interventions, a unique, de-identified ID that is common across data sources and is consistent with Health Insurance Portability and Accountability Act (HIPAA) standards is required. This is achieved through a process called tokenization.

10.4.1 Process and Methodology

Tokenization is the process of removal of identifiers from Personal Identifiable Information (PII) and replacing them with a unique token. A token is a universal, de-identified key that can be used to link subjects across datasets. Tokens are created based on elements of PII. Tokens are secure and can be consistently used without unblinding the trial or compromising the privacy of the trial subjects.

Tokens are irreversible and blinded, so subjects cannot be identified from such data. Tokens are created by mathematically scrambling PII into unique secure IDs (tokens) from which PII cannot be recovered. The tokens cannot be back engineered to identify the PII used to create the tokens, hence they protect subject privacy. Each token created is unique to the input PII, thus avoiding false matches. Multiple tokens can be created from different PII elements, improving the precision of matching. The same set of input PII will always create the same tokens, hence tokens are consistent.

Multiple tokens derived from different PII elements are created for each subject to enable accurate matching.

All subjects who have consented to participate in the trial will be given the opportunity to provide consent for tokenization. Participation in the tokenization is optional and subjects who decline to participate in the tokenization process will still be able to participate in the trial outside of the tokenization and linking to external databases. For subjects who provide consent to tokenization, no additional trial procedures beyond what is outlined in the protocol will be completed as a result of their participation in the tokenization.

The subject’s tokenized data will be available for linking to other future data for a period of 20 years. Only authorized sponsor personnel or their designees and authorized third

party vendors will have access to the tokens. Tokens will not be sold to any third parties, and they will not be used directly or indirectly to market any products.

10.4.2 Withdrawal of Subjects from Tokenization

Subjects can withdraw the consent for tokenization at any time prior to database lock. Database lock will occur after the end of the trial as referenced in Section 4.4. The trial subject would need to let the investigator know of their intent to withdraw consent for tokenization. If the withdrawal request reaches the sponsor before database lock, no tokens will be created for the subject and a communication will be sent to the investigator that the token will not be created. Tokens once created will be used. The sponsor will not be able to take back the subject's token that has already been created, since the parent PII information used to identify the trial subject will be destroyed and the sponsor will not be able to reidentify the trial subject. The sponsor cannot remove the subject data that is already part of larger datasets that have been and are being shared with other parties for further research.

Withdrawal of consent for participation in the trial does not mean withdrawal of consent for tokenization. To withdraw tokenization consent, the subject must contact their investigator.

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10.5 Appendix 5: Abbreviations

Abbreviation	Definition
AE	Adverse event
ADT	Antidepressant therapy
ATRQ	Antidepressant Treatment Response Questionnaire
CBT	Cognitive behavioral therapy
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impressions-Severity
CIOMS	Council for International Organizations of Medical Science
CRO	Clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CCI	[redacted]
DMC	Data Monitoring Committee
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition
ECT	Electroconvulsive therapy
EFMT	Emotional Faces Memory Task
eICF	Electronic informed consent
CCI	[redacted]
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
GAD-7	Generalized Anxiety Disorder-7
GCP	Good Clinical Practice
HAM-D_{17}	Hamilton Rating Scale for Depression, 17-item
CCI	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
iOS	iPhone operating system
IRB	Institutional review board
IRE	Immediately reportable event
LOCF	Last observation carried forward
M.I.N.I	Mini International Neuropsychiatric Interview
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	Missing at random
CCI	[redacted]
MDD	Major depressive disorder
MDE	Major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital - Antidepressant Treatment Response Questionnaire
MMRM	Mixed model repeated measurements
MNAR	Missing not at random

Abbreviation	Definition
OS	Operating system
PHQ-9	Patient Health Questionnaire-9
PII	Personal identifiable information
PP	Per-protocol
PQC	Product quality complaint
RWD	Real-world data
QMS	Quality management system
SAE	Serious adverse event
sham	A control that deploys only a working memory exercise
SIGH-D	Structured Interview Guide for the Hamilton Depression Rating Scale
SIGMA	Structured Interview Guide for the MADRS
SMS	Short message service
SMT	Shapes Memory Task
TEAE	Treatment-emergent adverse event
UADE	Unanticipated adverse device effect
US	United States
W	Week
WHODAS	World Health Organization Disability Assessment Schedule

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10.6 Appendix 6: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of CT-152 or sham used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

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