



Title: A Single Center Pilot Study to Evaluate Real Time Passive and Active High-Frequency Cognitive and Mood Assessment Data in Major Depressive Disorder Using Digital Wearable Technology

NCT Number: NCT03067506

Protocol Approve Date: 10 March 2017

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TAKEDA PHARMACEUTICALS

TAKEDA PHARMACEUTICALS PROTOCOL

A Single Center Pilot Study to Evaluate Real Time Passive and Active High-Frequency Cognitive and Mood Assessment Data in Major Depressive Disorder Using Digital Wearable Technology

Short Title: Cognitive and Mood Assessment Data in Major Depressive Disorder Using Digital Wearable Technology

Sponsor: Takeda Pharmaceuticals U.S.A., Inc.
One Takeda Parkway
Deerfield, IL 60015

Study Number: MDD-5003

IND Number: Not Applicable **EudraCT Number:** Not applicable

Compound: Not applicable

Date: 10 March 2017 **Version/Amendment Number:** 01

Amendment History:

Date	Amendment Number	Amendment Type	Region
08 December 2016	Initial version	Not applicable	United Kingdom
10 March 2017	01	Substantial	United Kingdom

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center (TDC) sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious prestudy event and serious adverse event reporting	Takeda Development Center (Americas) Pharmacovigilance Department Fax number: 224-554-1052
Adverse event, special situation reports and product quality issues	Email: PPD [REDACTED] Phone [REDACTED]
Medical Monitor (medical advice on protocol) and Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Takeda US Medical Affairs PPD [REDACTED]

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda Medical Officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

PPD	Date	PPD	Date
			

PPD	Date	PPD	Date
			

PPD	Date
	

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator ([Appendix B](#)).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix D](#) of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

CONFIDENTIAL

1.3 Protocol Amendment No. 01 Summary of Changes

This document describes changes in references to Protocol Incorporating Amendment No. 01 dated 28 February 2017.

The primary purpose of this amendment is to update the protocol to expand the selection criteria. Minor grammatical and editorial changes are included for clarification purpose only. Full details on changes of text are given in [Appendix E](#). The following is a summary of the changes made in the amendment:

1. Removed the requirement that subjects must have switched to a new antidepressant (monotherapy) for 24 weeks or less.

Rationale: This modification was deemed necessary to enhance enrollment into the study.

2. Removed the requirement that subjects must have been treated for more than a year without any period of remission.

Rationale: This modification was deemed necessary to enhance enrollment into the study.

3. Clarified the documentation requirements for the Screening Visit.

Rationale: To provide further clarification regarding the documentation required at the time of screening.

4. CCI 

Rationale: Clarification and update to the section to ensure accurate representation of protocol procedures and corrected the timing of the mood questions.

5. Removed reference to drug in Section 12.2.

Rationale: This is an unblinded noninterventional study.

6. CCI 

Rationale: Clarified the name of the scale.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda US Medical Affairs	Compound: Not applicable	
Title of Protocol: A Single Center Pilot Study to Evaluate Real Time Passive and Active High-Frequency Cognitive and Mood Assessment Data in Major Depressive Disorder Using Digital Wearable Technology	IND No.: Not Applicable	EudraCT No.: Not Applicable
Study Number: MDD-5003	Phase: Phase 4	
Study Design: The study is a single-arm, unblinded, 6-week prospective observational feasibility study, designed to assess the feasibility and compliance with a novel method for assessing mood and cognition in subjects with major depressive disorder (MDD). The study assesses the feasibility of and compliance with cognitive and mood testing using wearable technology and the correlation of mood and cognition outcomes on wearable technology with traditional objective neuropsychological cognitive function tests and self-reported mood outcomes. Thirty subjects aged between 18 and 65 years, inclusive, with mild-moderate depression prescribed second- or third-line antidepressant monotherapy will be recruited. Subjects will be provided with an Apple Watch on which brief cognitive and mood tests will be administered daily. Subjects will take part in up to 5 study visits, 1 in-person on-site visit, 3 web-based and 1 at home visit assessing performance on traditional objective neuropsychological cognitive function tests and self-reported measures of depression symptom severity and social function.		
Coprimary Objectives: To evaluate feasibility of and subject compliance with high-frequency testing of cognition and mood on wearable technology. Additionally to compare measures of mood and cognition on wearable technology against traditional objective neuropsychological cognitive function tests and self-reported measures of depression symptom severity outcome measures.		
Subject Population: Subjects aged 18 to 65 years, inclusive, with MDD.		
Number of Subjects: 30 subjects total	Number of Sites: Estimated total: 1 site	
Dose Level(s): Not applicable	Route of Administration: Not applicable	
Duration of Treatment: Not applicable	Period of Evaluation: 6 weeks	
Main Criteria for Inclusion: <ul style="list-style-type: none"> • The subject is a man or woman, aged 18 to 65 years, inclusive, and able to read and understand English. • The subject suffers from MDD as the primary psychiatric diagnosis. • The subject is currently being treated with an antidepressant (monotherapy). • The subject has scores on Patient Health Questionnaire-9 items (PHQ-9) ≥ 5 and PHQ-9 ≤ 15 at Screening. • In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements. • The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures, after the nature of the study has been explained according to local regulatory requirements. 		

Main Criteria for Exclusion:

- The subject has any current psychiatric disorder other than MDD (except nonprimary concurrent anxiety), other illness or condition that may compromise the study in the opinion of the investigator.
- The subject has a history of only responding to either combination or augmentation therapy in the current episode.
- The subject is considered to be at imminent risk for hospitalization due to severe depression in the opinion of the investigator. Recent hospitalization due to MDD within 3 months prior to Screening is also exclusionary.
- The subject has a significant risk of suicide according to the investigator's clinical judgment or has made an actual suicide attempt in the previous 6 months prior to Screening.

Main Criteria for Evaluation and Analyses:

The coprimary endpoints for this study are feasibility and compliance with testing on a wearable and correlations between measures obtained from the wearable technology compared with traditional objective neuropsychological cognitive function tests and self-reported measures of depression symptom severity outcome measures.

Statistical Considerations:

The coprimary aim is assessed by evaluating the number of wearable cognitive and mood assessments completed for each study day by the subject, as a proportion of the assessments requested.

Additionally the correlation between measures obtained on the wearable technology compared with traditional objective neuropsychological cognitive function tests and self-reported measures of depression symptom severity outcome measures will be assessed.

As this is a feasibility study, designed to guide future studies using this methodology, for the coprimary outcomes, inferential statistics will not be used, but the magnitude of correlations and rates of adherence will be described.

Sample Size Justification:

Using a sample size of 30, will be able to estimate a compliance rate of 80% to within a 95% CI of $\pm 12.8\%$. The proposed sample size also provides 80% power to detect correlations of $r=0.5$.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
CANTAB	Cambridge Neuropsychological Test Automated Battery
CRF	case report form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ERT	Emotion Recognition Test
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
MDE	major depressive episode
MDD	major depressive disorder

CCI
[Redacted]

PHQ-9	Patient Health Questionnaire—9 items
PPS	per protocol set
PRO	patient-reported outcomes
RVP	Rapid Visual Information Processing
SAE	serious adverse event
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
SWM	Spatial Working Memory

CCI
[Redacted]

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Major depressive disorder (MDD) is a leading cause of disability. The 12-month prevalence of MDD is approximately 7%, with more women than men affected [1]. The World Health Organization classified the disorder as the leading cause of years lost due to disability globally [2]. It is thought that cognitive impairment contributes significantly to this burden, offering a clinically relevant target for intervention.

4.1.1 Cognitive Impairment in MDD

Cognitive symptoms of depression (eg, difficulty concentrating or making decisions) are recognized as a core feature in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), and contribute to work-related disability and adverse psychosocial outcomes [3-9], beyond the impact of depressed mood. Cognitive deficits can be found in first-episode depression, and in recurrent depression both contribute to the risk of relapse, and worsen with repeated depressive episodes [10-14].

Cognition in depression is measured both through performance on objective cognitive tests and by patient-reported symptoms. The profile of cognitive impairment in depression is characterized by deficits in several domains, including processing speed, attention, executive function, and learning and memory [9,15-17]. However, there is poor correspondence between a patient's objectively measured cognitive function and patients' self-report [18,19], with the latter being affected by depressed mood. Therefore, both subjective and objective data need to be acquired as they provide complimentary clinically relevant information.

Cognitive dysfunction represents an underrecognized and undertreated aspect of depressive illness: when self-reported symptoms are examined, the majority of patients report impairment. In a prospective study of 267 subjects with MDD followed over 3 years while receiving treatment, the prevalence of symptoms of cognitive dysfunction was 94% during the acute phase of MDD and up to 44% during remission [13]. In a prospective, randomized, pragmatic clinical study of outpatients with nonpsychotic MDD (N=1426), the baseline prevalence of difficulty concentrating was 90%, with higher prevalence in those with repeated episodes [20]. On objective measurement using neuropsychological testing, cognitive dysfunction in depression is of moderate severity across multiple domains, with standardized effect sizes, ranging from 0.2 to 0.7 relative to unaffected controls [11,21-23]. There is increasing evidence that performance on standardized cognitive tests remains impaired even following remission of low mood in patients with MDD [12,21,24,25].

4.1.2 Functional Implications of Cognitive Dysfunction in MDD

Both objectively and subjectively measured cognitive difficulties impact daily function in patients with MDD, affecting function in work, home, and social settings, contributing to the disability burden of this disease. A multinational epidemiological study of 21,000 subjects [26] reported a

robust relationship between MDD and impaired home and occupational functioning. This was largely mediated by patient reported cognitive symptoms. Smaller studies have looked at the association between objectively measured cognitive function and functioning. Poorer objectively measured memory [27,28], attention, and executive function [18] have all been associated with impaired ability to perform activities of daily living in samples of individuals with MDD. Occupational performance is, perhaps unsurprisingly, associated with cognitive dysfunction across multiple cognitive domains [19,29,30]. Objective cognitive deficits are associated strongly to unemployment [19], and patient-reported cognitive symptoms impact on productivity and length of sick leave in a 2-year observational cohort study, even when controlling for depression severity [30]. Therefore, characterizing and treating these deficits has the potential to impact on functional outcomes and quality of life.

4.1.3 Assessment of Cognition and Mood on Mobile and Wearable Technology in Patients With Depression

One of the key obstacles to targeting the cognitive symptoms of depression is the lack of awareness from clinicians and patients of the presence of such impairments, and the lack of readily available tools for performing such assessments away from the clinic. The development of such tools has the potential to support the treatment and remediation of cognitive deficits associated with MDD. Mobile applications to assess patient-reported outcomes (PROs) are becoming increasingly acceptable in the context of clinical research, and have been used to track changes in mood in patients with depression [31-33], and as part of randomized-controlled studies to evaluate treatment efficacy [34].

Wearable technology such as smart watches are a more recent development, and therefore there are fewer examples of active measurement of cognition and symptoms on these wearables, although assessments of activity data from wrist-worn accelerometers have been found to be related to mood in patients with depression [35].

A recent feasibility study used the Microsoft band wearable technology to deliver an n-back test. The n-back is a measure of cognition, which asks participants to monitor a series of items briefly one at a time (in this case symbols) to detect a match “n” items ago. This task is nominally a test of working memory, requiring storage encoding and updating of a short-term store, but has been found to relate to a broad range of other cognitive domains including attention and executive function. The task has been extensively used in neuroimaging studies, which have shown performance to be related to a broad network of brain areas including prefrontal cortex, parietal lobe, and hippocampus [36]. Functional magnetic resonance imaging studies in depressed patients have shown that subjects recruited more resources within this same neural network to maintain a similar level of performance as controls. Data from the wearable instance of the n-back showed significant correlations with cognitive performance measured using the Cambridge Neuropsychological Test Automated Battery (CANTAB) battery of tests [37], suggesting that this may be a meaningful way of assessing cognition, which can be applied in patients with depression to track cognition.

4.2 Rationale for the Proposed Study

Cognitive problems are common in major depression and are under recognized by both patients and clinicians. High-frequency, near-patient, cognitive testing provides the opportunity to detect and understand the pattern of cognitive symptoms, to maximize patient engagement with treatment and to inform clinicians regarding the severity, impact, and time course of cognitive deficits in patients with depression. The present study aims to assess the feasibility and compliance of an assessment of cognitive function and mood implemented on a smart watch in subjects with depression, with the goal of being as sensitive as the external traditional objective neuropsychological cognitive function tests and self-reported measures of depression symptom severity outcome measures) measures of cognition in detecting and understanding the change in cognitive function and the potential of developing a method for assessing cognition and mood in subjects undergoing treatment with antidepressant medication in clinical or research settings.

4.3 Benefit/Risk Profile

Not applicable.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Coprimary Objectives

- To evaluate feasibility of and subject compliance with high-frequency testing of cognition and mood on wearable technology.
- To compare measures of mood and cognition on wearable technology against traditional objective neuropsychological cognitive function tests and self-reported measures of depression symptom severity outcome measures.

5.1.2 Additional Objectives

- CCI
-

5.2 Endpoints

5.2.1 Coprimary Endpoints

- Compliance with daily wearable testing, defined as number of tests completed over the 6-week study period.
- Correlations between measures of cognition on the wearable technology (n-back d') and performance on the CANTAB tests.

5.2.2 Additional Endpoints

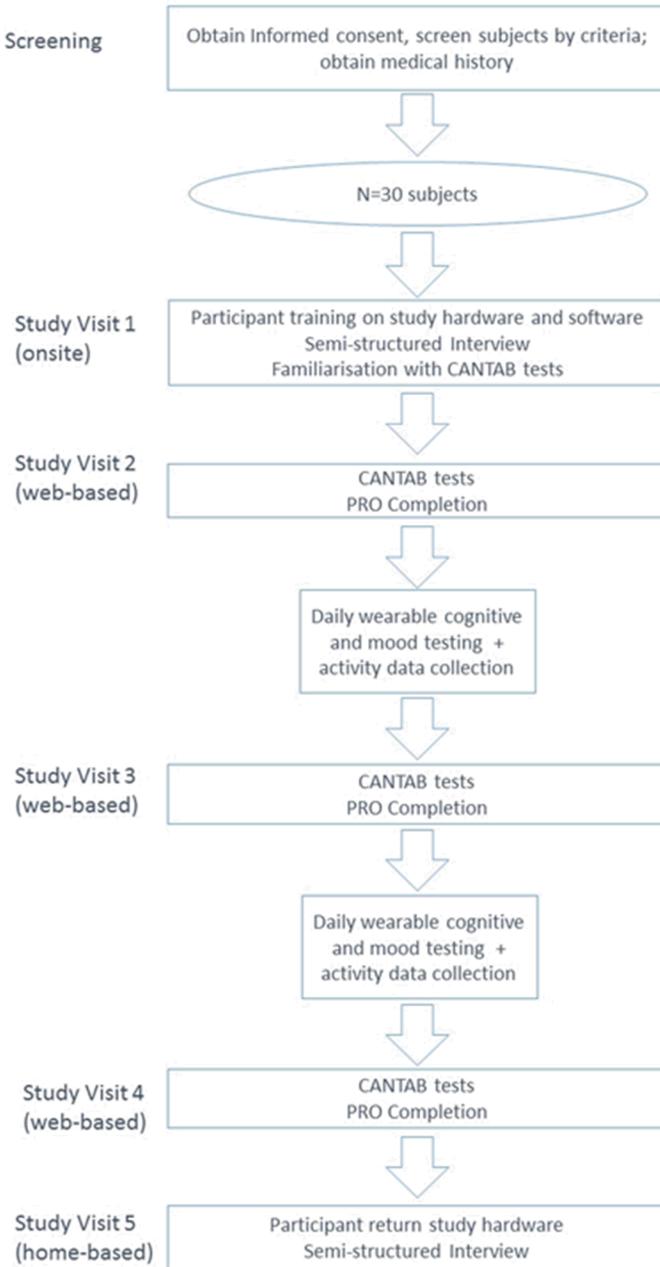
- CCI
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-

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

The study is a single-arm, unblinded, 6-week prospective observational feasibility study, designed to assess the feasibility and compliance with a novel method for assessing mood and cognition in subjects with MDD. The study assesses the feasibility of and compliance with cognitive and mood testing using wearable technology and the correlation of mood and cognition outcomes on wearable technology with traditional objective neuropsychological cognitive function tests and self-reported mood outcomes. Thirty subjects aged between 18 and 65 years, inclusive, with mild-moderate depression prescribed second- or third-line antidepressant monotherapy will be recruited. Thirty subjects will be provided with an Apple Watch on which brief cognitive and mood tests will be administered daily. All subjects will take part in up to 5 study visits, 1 in-person on-site visit, 3 web-based and 1 at home visit, assessing performance on traditional objective neuropsychological cognitive function tests and self-reported measures of depression symptom severity and social function. A schematic of the study design is included as [Figure 6.a](#). A schedule of assessments is listed in [Appendix A](#).

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

The study population consists of patients with mild-moderate depression, aged between 18 and 65 years, inclusive. The study is a single-arm, unblinded, prospective feasibility study, designed to assess the feasibility and compliance with, a novel method for assessing mood and cognition in subjects with MDD. The proposed sample size is 30 subjects.

The wearable technology chosen for this study is the Apple Watch. This has a high-resolution display, which enables the presentation of stimuli and a touch screen for the collection of participant responses. The cognitive task employed on the wearable is the n-back test [38]. This task has been previously used in studies of daily cognitive testing over 100 study days in older adults and in a prior feasibility study on a wearable technology in healthy participants, where it was found to correlate with performance on CANTAB tasks of working memory, executive function, and processing speed [37,39]. On average, in this study participants completed 2 assessments on the wearable each day, although the length of the study was shorter than in the current protocol at only 2 weeks. The length of the present study, over 6 weeks, corresponds to the time period over which response to antidepressant pharmacotherapy shows its efficacy in treating the mood symptoms of MDD. If the wearable technology assessments being developed are to be effective in monitoring changes to cognitive symptoms following treatment, it should be useable by patients over a similar time frame.

The recruitment of subjects with mild-moderate depression represents the most common range of severity encountered in clinical practice. Participants with this degree of depression are likely to show cognitive deficits, and therefore provide an insight into performance and compliance with the study. The sample size selected is based on the compliance and magnitude of correlations observed in our previous research [37].

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study product that indicates a change in the known risk/benefit profile for the product, such that the risk /benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to study entry.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. The subject is a man or woman, aged 18 to 65 years, inclusive, and able to read and understand English.
2. The subject suffers from MDD as the primary psychiatric diagnosis.
3. The subject is currently being treated with an antidepressant (monotherapy)
4. The subject has scores on PHQ-9 ≥ 5 and PHQ-9 ≤ 15 at Screening.
5. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
6. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures, after the nature of the study has been explained according to local regulatory requirements ([Appendix B](#)).

7.2 Exclusion Criteria

1. The subject reports any current psychiatric disorder other than MDD (except nonprimary concurrent anxiety), other illness, or condition that may compromise the study in the opinion of the investigator.
2. The subject is not currently receiving an antidepressant at the time of Screening.
3. The subject is considered to be at imminent risk for hospitalization due to severe depression in the opinion of the investigator. The subject has been hospitalized due to MDD within 3 months prior to Screening.
4. The subject has a significant risk of suicide according to the investigator's clinical judgment or has made an actual suicide attempt in the previous 6 months prior to Screening.
5. The subject has a history of only responding to either combination or augmentation therapy in the current episode.
6. The subject has received any investigational compound within 30 days prior to Screening or 5 half-lives prior to Screening, whichever is longer.
7. The subject is currently participating in another clinical study.
8. The subject has participated in 2 or more interventional clinical studies in the year prior to Screening, or has participated in a clinical study for a psychiatric condition that is exclusionary per this protocol.

9. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling).
10. The subject reports 1 or more of the following:
 - a) Current or history of: manic or hypomanic episode, schizophrenia or any other psychotic disorder, including schizoaffective disorder, major depression with psychotic features, bipolar depression with psychotic features, obsessive compulsive disorder, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in DSM-5.
 - b) Current diagnosis or history of alcohol or other substance abuse or dependence (excluding nicotine or caffeine).
 - c) Presence or history of a clinically significant neurological disorder (including epilepsy).
 - d) Neurodegenerative disorder (Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease, etc).

7.3 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the case report form (CRF) using the following categories. For screen failure subjects, refer to Section 9.1.9.

1. Serious prestudy event or serious adverse event (SAE). The subject has experienced a serious prestudy event or SAE that prevents full participation in the study or the subject is unwilling to continue because of the serious prestudy event or SAE.
2. Significant protocol deviation. The discovery that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.

6. Other.

Note: The specific reasons should be recorded in the “specify” field of the CRF.

7.4 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject’s study participation at any time during the study when the subject meets the study termination criteria described in Section 7.3. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject’s participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Materials

8.1.1 Ancillary Materials

Subjects will be provided with an Apple Watch Series 1, a black sports band, and charging cable. This is a wearable, paired with an iPhone, which contains a range of sensors, including accelerometers and heart rate sensors. The study software measuring cognition (n-back) and mood will be installed. Subjects will sign for the wearable at the start of the study, and return the wearable at the Final Visit or Early Termination Visit. Researchers will sign for the return of the wearable.

8.1.2 Storage

Prior to subjects receiving the wearable technology they will be kept in an appropriate, limited-access, secure place until they are used or returned to the sponsor or designee.

8.1.3 Accountability and Return of Ancillary Materials

Apple watches will be counted and reconciled at the site before being returned to the supplier.

The investigator or designee must ensure that the sponsor-supplied Apple watches are used in accordance with the protocol and is provided only to subjects enrolled in the study. To document appropriate use of the Apple watch the investigator or designee must maintain records of all sponsor-supplied materials to the site, site inventory, dispensation and use by each subject, and return to the supplier.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee may perform accountability and reconciliation before sponsor-supplied materials are returned to the supplier. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied accountability, return, and originals will be sent to the sponsor or designee as applicable.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in [Appendix A](#).

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section [15.2](#).

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed. A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include age, as described by the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.4](#)). Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 6 months prior to signing of informed consent.

9.1.3 Documentation of Concomitant Medications

Concomitant medication is any drug given during the observational study period. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the CRF.

9.1.4 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. The condition (ie, diagnosis) should be described.

9.1.5 Procedures for Clinical Laboratory Samples

Not applicable.

9.1.6 Contraception and Pregnancy Avoidance Procedure

There are no requirements for contraception or pregnancy avoidance. Subjects should follow the instruction according to label for their prescribed antidepressant.

9.1.7 Pregnancy

Women of childbearing potential may be included in this study.

9.1.8 Electrocardiogram Procedure

Not applicable.

9.1.9 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is withdrawn at the Screening Visit after signing the informed consent, the investigator should complete the CRF.

The primary reason for screen failure is recorded in the CRF using the following categories:

- Serious prestudy event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria, specify reason.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal, specify reason.
- Study termination.

Subject identification numbers assigned to subjects who fail screening should not be reused.

9.1.10 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the observational study period. If the subject is found to be not eligible for entrance, the investigator should record the primary reason for failure on the applicable CRF.

9.1.11 Wearable Technology Data

Subjects will be given an Apple Watch on which cognitive assessment and mood assessment will be carried out. Subjects will be asked to wear the watch between 8 AM and 10 PM daily for the 6-week study period. All subjects will be prompted to complete cognitive and mood assessments on 3 occasions across the day. Two occasions (morning and afternoon) will comprise assessment of cognition, and the final assessment in the evening will constitute a review of the day focusing on self-reported depressed mood. For all subjects, passive sensor data will also be acquired via the Apple Watch to assess physical activity.

9.1.11.1 *Wearable Cognitive Assessment*

The 2-Back is a working memory test in which 30 symbols are presented visually. Subjects are asked to make a response when the symbol is the same as that presented 2 earlier. The load on working memory reflects the ordering, retention, updating, and manipulation of 2 symbols and consideration of the relationship to a third newly presented symbol, which could have been a target or a nontarget. From this test, latency and d' measure accuracy, which is the ratio hits (correct detection of an n-back match) and false alarms (responding when no n-back match was present) are calculated.

9.1.11.2 ^{CCI}
^{CCI}

9.1.11.3 ^{CCI}
^{CCI}

9.1.12 Subject Self-Report Measures

9.1.12.1 ^{CCI}
^{CCI}

9.1.12.2 *Perceived Deficits Questionnaire Attention/Concentration and Planning/Organization Subscore*

^{CCI}

CCI

9.1.12.3 CCI

CCI

9.1.13 CANTAB Cognitive Assessments

The CANTAB is a computer-based cognitive assessment system consisting of a battery of neuropsychological tests, tapping distinct cognitive domains. The tests to be used in the present study are described in Sections 9.1.13.1 to 9.1.13.3. The CANTAB Cognitive Assessments will be administered via the Cantab Connect web-based testing interface. Subjects will be sent a unique link to a secure web-page delivering the tests.

9.1.13.1 Emotion Recognition Test

The Emotion Recognition Test (ERT) measures emotion processing bias. This task briefly presents subjects with morphed composite faces representing faces showing emotions of different intensities, and asks them to detect the emotions presented. As the intensity of the emotion decreases, the ability of subjects to detect the portrayed emotion decreases. Outcomes are accuracy of responses for each emotional expression

9.1.13.2 Spatial Working Memory

CANTAB–Spatial Working Memory (SWM) assesses a subject’s retention of spatial information, ability to manipulate remembered items, and strategize. The subject is asked to find tokens in on-screen boxes and move them. Difficulty ranges from 4 to 8 box assessments, 2 trials for each assessment. Possible errors for each successful assessment: 4 box 0-38; 6 box 0-58; 8 box 0-78. Between Errors for N Boxes is the cumulative number of errors per each successful study. Total scores range from 0 to 175. Lower scores indicate better performance. Strategy score is the number of unique boxes the subject searched in the two 6 and 8 box trials. The 6 box trial scores ranges from 1 (1 box searched for all 6 tokens) to 6 (6 boxes searched for 6 tokens). The 8 box trial score ranges from 1 (1 box searched) to 8 (8 boxes searched for 8 tokens). The total of the 4 trial scores ranges from 4 to 28. A lower score indicates better performance.

9.1.13.3 The Rapid Visual Information Processing

The Rapid Visual Information Processing (RVP) test from the CANTAB test battery is a measure of sustained attention. A white box appears in the center of the computer screen, inside which digits, from 2 to 9, appear in a pseudo-random order, at the rate of 100 digits per minute. Subjects are requested to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8) and to register responses using the press pad. The administration time is 10 minutes. The main outcome measure is A': a signal detection measure of sensitivity to the target, regardless of response tendency (expected range is 0.00 to 1.00). Median latency: The median response latency during assessment sequence blocks where the subject responded correctly.

9.1.14 Semistructured Interviews

Semistructured interviews will be carried out by trained researchers, according to prespecified interview templates. Interviews will be digitally recorded and researchers will take notes to aid in the analysis and interpretation of the interviews as outlined in Section [13.1.5](#).

9.1.14.1 Study Entry Interview

Short semistructured interviews will be carried out to explore a subject's expectations around the assessments on the Apple Watch, their motivations for taking part, and their understanding of cognition and cognitive testing.

9.1.14.2 End of Study Interview

A 90-minute semistructured interview done as home based visit will explore subject's experience of assessment on the wearable technology over time, any changes in motivation and compliance, and the contextual factors that might have contributed to those changes. The purpose of the home visit is to explore in depth the factors that impact people's compliance and motivation with high-frequency cognitive and mood testing. Since these visits will take place in the context of people's use of the wearable and cognitive and mood assessments during the trial period, they will enable the researchers to draw on the range of these contextual elements during the semi-structured interview. As such, it will allow the researcher to observe qualitative issues that participants might not have deemed important, and as a result identify drivers or barriers that might otherwise be forgotten or missed outside of this real world setting.

9.2 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in [Appendix A](#). Assessments should be completed at the designated visit/time point(s).

9.2.1 Screening

Subjects will be screened within 21 days prior to Baseline. Procedures to be completed during the Screening Visit are detailed in [Appendix A](#). Subjects will be screened in accordance with

predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.9 for procedures for documenting screening failures.

Procedures to be completed at Screening include:

- Informed consent.
- Demographics, medical history, and medication history.
- Concomitant medications.
- Concurrent medical conditions.
- PHQ-9.
- Serious prestudy event assessment.

9.2.2 Study Entrance (Visit 1)

Study entrance will take place on Day 1. The following procedures will be performed and documented at Study Entrance:

- Assigned to study training on the use of the Apple Watch.
- Training on the CANTAB tests.
- Semistructured interview (Section 9.1.14.1).
- Serious prestudy event assessment.
- AE assessment.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria the subject will be enrolled in the study. The procedure for documenting screening failures is provided in Section 9.1.9.

9.2.3 Visits 2, 3, and 4

Subjects will log on to a secure study site hosting the CANTAB tests (Section 9.1.13) and self-report measures (ie, CCI) (Section 9.1.12), which they will complete from home. Subjects will be instructed to select a quiet time to complete these tests when they will not be distracted.

9.2.4 Phone Contacts: Reminder and Support Calls

Reminder calls will be carried out during the study when the system detects that the cognitive task has not been completed in the same day or previous evening. The purpose is to check for the presence of technical difficulties with the watch or application software, or other barrier to compliance. The study also provides a support number for subjects to call should they experience any technical difficulties with the study hardware or software.

Researchers will follow a script to facilitate the collection of relevant compliance information. Subject responses will be written down. Any unsolicited safety information described by the subject will be documented in the CRF and not written on the script used for the telephone call, and will be dealt with according to study AE reporting procedures.

9.2.5 Final Visit or Early Termination

The Final Visit will be a home based visit and will be performed on Study Day 44 (± 3 days) or at the Early Termination Visit. The following procedures will be performed and documented:

- Collection of the Apple Watch from subjects.
- Semistructured interview (Section [9.1.14.2](#)).
- Concurrent medical conditions.
- AE assessment.

9.2.6 Poststudy Care

The Apple Watch will not be available upon completion of the subject's participation in the study.

9.3 Biological Sample Retention and Destruction

No biological samples will be collected.

10.0 PRESTUDY EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Prestudy Event

A prestudy event is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to study start; it does not necessarily have to have a causal relationship with study participation. In this study only prestudy events that meet serious criteria will be collected.

10.1.2 AEs

An AE is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a Takeda medicinal product, whether or not the event is considered causally related to the use of the Takeda product.

10.1.3 Special Situation Reports and Product Quality Issues

A special situation report (SSR) includes any of the following events:

- **Pregnancy:** Any case in which a pregnancy patient is exposed to a Takeda product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- **Breastfeeding:** Infant exposure from breast milk.
- **Overdose:** All information of any accidental or intentional overdose.
- **Drug abuse, misuse or medication error:** All information on medicinal product abuse, misuse or medication error (potential or actual).
- **Suspected transmission of an infectious agent:** All information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- **Lack of efficacy of Takeda product.**
- **Occupational exposure.**
- **Use outside the terms of the marketing authorisation, also known as “off-label”.**
- **Use of falsified medicinal product.**

A product quality issue refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

10.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence during the study:

1. Results in DEATH.
2. Is LIFE THREATENING.
 - The term “life threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

Events that occur after the informed consent has been signed but before the study begins that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections [10.2.3](#) and [10.3](#)).

10.1.5 Severity of Prestudy Events and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject’s usual activities.
Severe:	The event causes considerable interference with the subject’s usual activities.

10.1.6 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all SAEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.7 Start Date

The start date of the SAE/prestudy event is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.8 Stop Date

The stop date of the SAE/prestudy event is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.9 Frequency

Episodic SAEs/prestudy events or those that occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.10 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the SAE/prestudy event.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular SAE/prestudy event with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular SAE/prestudy event state remaining “Not recovered/not resolved”.
- Resolved with sequelae – the subject recovered from an acute SAE/prestudy event but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the SAEs/prestudy event which are considered as the cause of death.
- Unknown – the course of the SAE/prestudy event cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of Spontaneous AEs, SSRs, and Product Quality Issues Related to a Takeda Product

If during the conduct of the study, a health care professional or patient spontaneously reports an AE, SSR, or product quality issue where the event/issue pertains to a Takeda product (or unbranded generic); such information should be reported to the sponsor. As such reports are spontaneously notified, causality of any AEs should be assumed unless there is evidence to the contrary.

Adverse events, special reporting situations or products complaints relating to any Takeda UK products received spontaneously must be reported to ^{PPD} [REDACTED] or by telephone

(PPD) within 24 hours of awareness and no later than by the next working day. The preferred method for reporting is via email. If a report is received via telephone it should be backed up with an email.

10.2.2 Serious Prestudy Event and SAE Collection Period

Collection of SAEs will commence from the time the subject signs the informed consent to participate in the study and continue until the end of the study.

At each face to face (in-person) study visit, the investigator will assess whether any SAEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report spontaneous AEs occurring at any other time during the study. Subjects experiencing a serious prestudy event must be monitored until the symptoms subside or there is a satisfactory explanation for the change. Nonserious prestudy events, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing SAEs, whether considered associated with the study procedures or not, must be monitored until the symptoms subside and or until there is a satisfactory explanation for the changes observed. All serious prestudy events and SAEs that occur during the study period will be documented in the CRF, whether or not the investigator concludes that the event is related to the study procedures. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Intensity.
5. Investigator’s opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Outcome of event.
7. Seriousness.

10.2.3 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator’s name.

- Relationship to study procedure.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of serious prestudy events will follow the procedure described for SAEs.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form (or provide other written documentation and fax it within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, electrocardiograms, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor is responsible for submission of AEs and SSRs to regulatory authorities in accordance with local reporting requirements or the sponsor's postmarketing commitments.

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment or consider changes in overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC.

11.0 STUDY-SPECIFIC COMMITTEES

Not applicable

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan or equivalent.

12.1 CRFs (Paper)

Completed CRFs are required for each subject.

The study site will supply CRFs for use during the study. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities, as applicable. CRFs must be completed in English. All paper CRFs must be filled out legibly in black or blue ballpoint ink (use of black ink is preferred).

Corrections are to be made by making a single-line strikeout of the incorrect information and writing in the revisions. All corrections must be initialed and dated. Reasons for significant corrections should additionally be included. All new additions are to be made with the date and sign, or sign and seal affixed. Corrections to eCRFs will be made directly in the system, and an audit trail of changes will be maintained at the site.

The principal investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After submission of the CRFs to the sponsor, any change of, modification of or addition to the data on CRFs should be made by the investigator with use of change and modification records of CRFs (Data Clarification Form). The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign, or sign and seal, and date the form.

After the lock of the study database, any change of, modification of or addition to the data on the CRFs should be made by the investigator with use of change and modification records of the CRFs.

CRFs may be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee, as applicable. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), and copies of all paper CRFs and query responses to enable evaluations or audits from regulatory

authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. A data review may be conducted prior to database lock to assess completeness of the study database and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The full analysis set (FAS) is defined as all subjects who completed the Study Entrance Visit and received a study wearable technology with at least 1 day of assessments completed. This will be the data set for primary analysis. In this study, 2 kinds of analysis sets are defined: FAS, and safety analysis set. The definition of each analysis set will be described in the Handling Rules for Analysis Data or equivalent.

The safety set will include all subjects who were enrolled and completed the Study Entrance Visit. It is likely that the safety set will be the same as the FAS.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, with consulting a medical expert as needed. If necessary, the Handling Rules for Analysis Data will be supplemented with new handling rules that were not discussed at the planning stage. The Handling Rules or equivalent for Analysis Data must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Summary statistics (mean, SD, median, minimum, and maximum) for age, length of major depressive episode (MDE), number of prior MDEs, scores on PROs (CCI [REDACTED]), scores on CANTAB cognitive test measures at enrollment will be calculated. Distributions of subjects by sex, and antidepressant class may be summarized if applicable.

Demography tables will be presented for the all enrolled set and the per protocol set. Detailed subject listings will be located in the appendices.

13.1.3 Analysis of Wearable Technology Data Collection Compliance (Coprimary Aim)

This is a coprimary study endpoint, and will be analyzed by assessing the number of wearable cognitive and mood assessments completed for each study day by the subject, as a proportion of the assessments requested. For each subject the percentage of study wearable assessments completed will be calculated and reported in tables overall and as a function of study day.

13.1.4 Analysis of Validity of Wearable and Mood Testing (Coprimary Aim)

This corresponds to the other coprimary aim of the study. Individual subject data on the wearable n-back cognitive test will be analyzed using a longitudinal nonlinear mixed model approach,

which characterizes subject performance as a combination of an intercept and a slope, representing their overall ability and a learning effect, thereby reducing the dimensionality of the cognitive data. These derived cognitive performance parameters from the n-back will be correlated with performance on CANTAB measures of working memory (SWM), attention and concentration (RVP), and executive function (CANTAB SWM Strategy and One Touch Stockings) and [REDACTED], using a Pearson correlation coefficient, or nonparametric equivalent, depending on the observed distribution of data. These are the cognitive domains believed to be assessed by the n-back test.

[REDACTED]

coefficients observed, rather than significance levels. No inferential statistical tests will be carried out, and therefore no adjustment for multiple comparisons is required.

13.1.5 Qualitative Analysis

Qualitative assessment of factors relating to compliance will be obtained from the examination of themes emerging from 3 sources:

1. Semistructured study entry interviews (Section 9.1.14.1 Study Day 1) focusing on subject's expectations, motivation, and understanding around cognitive testing and technology.
2. Study technical support queries and logs of within-study subject interactions from phone contacts (Section 9.2.4)
3. Semistructured end of study interviews (Section 9.1.14.2 Final Visit, Study Day 44) exploring subjects' experience of the application over time, any changes in motivation and compliance, and the contextual factors that might have contributed to those changes.

Interpretative Phenomenological Analysis will be used to analyze the qualitative data. To increase the rigor and validity of the analysis, and as a form of triangulation, the analysis will be conducted by 3 members of the research team (the lead qualitative researcher and 2 others). Analysis will involve 2 stages:

1. Data management, which will include:
 - a) Familiarization with the data, reading notes, and/or listening to the audio dialogue in order to extract main themes and ideas.
 - b) Thematic framework development, identifying the key issues and concepts present in the data and creating themes both inductively, based on the data, and deductively, based on the research questions.
2. Interpretation stage, which will include focused defining the main concepts and mapping the ways in which different parts of the data are related to each other.

13.1.6 Safety Analysis

AEs will be summarized using the safety set. No statistical testing or inferential statistics will be generated. Data will be summarized using preferred term and primary system organ class.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The proposed sample size of 30 is commensurate with usual practice for feasibility studies [40]. Using a sample size of 30, will be able to estimate a compliance rate of 80% to within a 95% CI of $\pm 12.8\%$. The proposed sample size also provides 80% power to detect correlations of $r=0.5$, as per the secondary outcomes.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site may be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents may be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. The investigator will conduct the study according to applicable local regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix B](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol’s review and approval. This protocol, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator’s final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to

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the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

Study Day/Week:	Screening	Baseline	Day 2 (Web-based)	Week 3 (Web-based)	Week 6 (Web-based)	Final Visit or Early Termination Visit (In- person Home Based) Week 6 (b)
	Days -21 to -1	Day 1 (In-person) (a)				
Visit Windows (Days):			1 to 2	18 to 24	40 to 46	41 to 47
Visit Number:	-1	1	2	3	4	5
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics and medical history	X					
Medication history	X					
Concomitant medications	X	X				X
Concurrent medical conditions	X	X				
CCI						
CANTAB cognitive testing			X	X	X	
CCI						
CCI						
Semistructured interview		X				X
Provide subjects with study wearable technology and training		X				
Wearable cognitive and mood assessment			-----	-----	-----	
Wearable activity measurement (includes HR)			-----	-----	-----	
Return of study wearable						X
Serious Prestudy event assessment	X	X				
AE assessment		X	X	X	X	X

(a) In-person on site visit.

(b) Conduct face to face (in person-home based) Final Visit procedures for subjects discontinued early per Section 7.4. The end of study is defined as the date of the last visit (Day 44) of the last subject undergoing the study unless the study is stopped earlier by the sponsor.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the developing a better understanding of disease, studying other therapies for patients, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
 - e) that the subject's identity will remain confidential in the event that study results are published.

25. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies. Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 01.

Pages 10 and 22, Sections 2.0, 7.1, and 7.2

Existing Text

Inclusion Criteria

3. The subject *has been* treated *previously* with *at least 1* antidepressant (monotherapy) *and has been switched to a new antidepressant (monotherapy) for 24 weeks or less.*

Exclusion Criteria

2. The subject *has not switched antidepressants in the past and/or* is not currently receiving an antidepressant at the time of Screening.

Revised Text

Inclusion Criteria

3. The subject **is currently being** treated with **an** antidepressant (monotherapy).

Exclusion Criteria

2. The subject is not currently receiving an antidepressant at the time of Screening.

Rationale for Amendment

This modification was deemed necessary to enhance enrollment into the study.

Pages 11 and 22, Section 2.0 and 7.2

Existing Text

5. The subject has a history of only responding to either combination or augmentation therapy in the current episode *and has had been treated for more than a year without any period of remission.*

Revised Text

5. The subject has a history of only responding to either combination or augmentation therapy in the current episode.

Rationale for Amendment

This modification was deemed necessary to enhance enrollment into the study.

Page 27, Section 9.1.9

Existing Text

Investigators must account for all subjects who sign informed consent. If the subject is withdrawn at the Screening Visit, the investigator should complete the CRF.

CONFIDENTIAL

Revised Text

Investigators must account for all subjects who sign informed consent. If the subject is withdrawn at the Screening Visit **after signing the informed consent**, the investigator should complete the CRF.

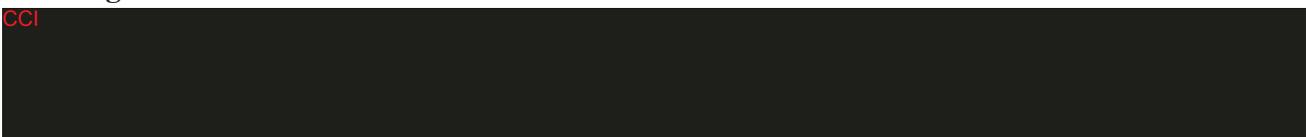
Rationale for Amendment

To provide further clarification regarding the documentation required at the time of screening.

Page 28, Section 9.1.11.2

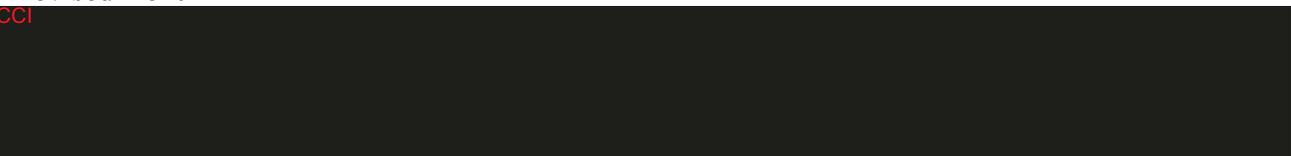
Existing Text

CCI



Revised Text

CCI



Rationale for Amendment

Clarification and update to the section to ensure accurate representation of protocol procedures and corrected the timing of the mood questions.

Page 39, Section 12.2

Existing Text

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), copies of all paper CRFs and query responses, *and detailed records of drug disposition* to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

Revised Text

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms),

and copies of all paper CRFs and query responses to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

Rationale for Amendment

This is an unblinded noninterventional study.

Page 42, Section 13.1.4

Existing Text

These derived cognitive performance parameters from the n-back will be correlated with performance on CANTAB measures of working memory (SWM), attention and concentration (RVP), and executive function (CANTAB SWM Strategy and One Touch Stockings) and self-reported ratings of cognitive symptoms (*Cognitive Dysfunction Questionnaire*), using a Pearson correlation coefficient, or nonparametric equivalent, depending on the observed distribution of data.

Revised Text

These derived cognitive performance parameters from the n-back will be correlated with performance on CANTAB measures of working memory (SWM), attention and concentration (RVP), and executive function (CANTAB SWM Strategy and One Touch Stockings) and self-reported ratings of cognitive symptoms (CCI), using a Pearson correlation coefficient, or nonparametric equivalent, depending on the observed distribution of data.

Rationale for Amendment

Clarified the name of the scale.

Amendment 01 to A Single Center Pilot Study to Evaluate Real Time Passive and Active High-Frequency Cognitive and Mood Assessment Data in Major Depressive Disorder Using Digital Wearable Technology

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Medical Affairs Approval	13-Mar-2017 15:25 UTC
	Clinical Operations Approval	13-Mar-2017 22:40 UTC
	Biostatistics Approval	14-Mar-2017 12:48 UTC
	Clinical Science Approval	14-Mar-2017 13:43 UTC
	Pharmacovigilance Approval	16-Mar-2017 14:23 UTC