Otsuka Pharmaceutical Development & Commercialization, Inc.

Aripiprazole (OPC-14597) Digital

CLINICAL PROTOCOL

Protocol Title: An Open-label, Prospective Trial Assessing Positive Detection Accuracy and Detection Latency Measures of the Miniature Ingestible Event Marker Tablet Using the D-Tect Patch in Healthy Subjects and Assessing Detection Latency Measures Using the D-Tect Patch in Subjects With Serious Mental Illness Taking Abilify MyCite Tablet

Protocol Lay Person Short Title: A Trial to Assess a Wearable Patch's Functioning to Detect Medication Ingestion

Protocol No. 031-201-00521

CONFIDENTIAL — PROPRIETARY INFORMATION

Trial Type:	Interventional
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States

CCI [redacted]

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Abbreviation	Definition
AE	Adverse event
App	Application
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Science
COVID-19	Coronavirus disease 2019
DMS	Digital Medicine System
DOI	Directly observed ingestion
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identifier
IEM	Ingestible event marker
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MIT	Miniature ingestible event marker tablet
PDA	Positive detection accuracy
PQC	Product Quality Complaint
QC	Quality control
SAE	Serious adverse event
SMI	Serious mental illness
SmPC	Summary of Product Characteristics
SN	Serial number
SoA	Schedule of assessments
US	United States
USPI	United States Prescribing Information
WSs	Wearable sensors

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1 Protocol Summary

1.1 Synopsis

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

Name of Investigational Device: Digital Medicine System (D-Tect Patch and Ingestible Event Markers [Miniature Ingestible Event Marker Tablet or Abilify MyCite Tablet])

Protocol No.: 031-201-00521

Protocol Title: An Open-label, Prospective Trial Assessing Positive Detection Accuracy and Detection Latency Measures of the Miniature Ingestible Event Marker Tablet Using the D-Tect Patch in Healthy Subjects and Assessing Detection Latency Measures Using the D-Tect Patch in Subjects With Serious Mental Illness Taking Abilify MyCite Tablet

Protocol Lay Person Short Title: A Trial to Assess a Wearable Patch's Functioning to Detect Medication Ingestion

Trial Type: Interventional

Planned Treatment/Indication: Not applicable.

Trial Rationale:

This two-cohort, open-label, prospective trial is designed to assess the positive detection accuracy (PDA) and detection latency of the D-Tect Patch.

The PDA is defined as the proportion of miniature ingestible event marker tablets (MITs) detected out of the total ingestible event marker detections of tested D-Tect Patches (Cohort 1 only).

For detection latency, Patch Detection Latency, Ingestion Data Transfer Latency, and Total Detection Latency will be measured for both cohorts (ie, MITs and Abilify MyCite). See Section 2 for the definition of the detection latency metrics.

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Objectives and Endpoints:

Objectives	Endpoints
Primary: • Evaluate PDA and detection latency measures for the D-Tect Patch.	PDA: Estimate PDA with the CI lower limit greater than 95% when a subject is wearing the D-Tect Patch. Detection Latency: The median Patch Detection Latency, Ingestion Data Transfer Latency, and Total Detection Latency.
Secondary: • To collect and characterize adverse events associated with the device.	Safety: The frequency and severity of AEs, device-related AEs, SAEs, AEs leading to discontinuation, and unanticipated adverse device effects.

AE = adverse event; CI = confidence interval; PDA = Positive Detection Accuracy; SAE = serious adverse event.

Trial Design:

This is a two-cohort, open-label, prospective trial designed to assess the PDA and detection latency of the D-Tect Patch.

Trial Population:

Two cohorts of subjects will be enrolled in this trial.

Cohort 1: A minimum of 24 healthy subjects will be tested to obtain a minimum of 360 miniature ingestible event marker tablet ingestions for Cohort 1. Healthy subjects will be drawn from nonvulnerable subpopulations. If a subject fails to complete participation in the testing, for whatever reason, a new, qualified candidate may be enrolled as a replacement.

Cohort 2: A minimum of 30 subjects with serious mental illness (SMI) will be tested to obtain a minimum of 30 Abilify MyCite ingestions for Cohort 2. These subjects will ingest Abilify MyCite at the same dose as their currently prescribed aripiprazole. If a subject fails to complete participation in the testing, for whatever reason, a new, qualified candidate may be enrolled as a replacement.

Key Inclusion/Exclusion Criteria:

Cohort 1: Male and female subjects greater than or equal to the age of 18 years, who are in good health, and who are able to provide informed consent will be considered for inclusion in the trial. Subjects with difficulty swallowing, active skin infection or history of inflammatory skin condition, or an allergy to adhesive bandages/tapes will be excluded from participation.

Cohort 2: Male and female subjects with SMI greater than or equal to the age of 18 years who are currently prescribed and taking aripiprazole and who are able to provide informed consent will be considered for inclusion in the trial. For the purposes of this

trial, SMI refers to subjects with a diagnosis of Schizophrenia, Major Depressive Disorder, or Bipolar I Disorder per Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-5) criteria. Subjects with difficulty swallowing, active skin infection or history of inflammatory skin condition, or an allergy to adhesive bandages/tapes will be excluded from participation.

Trial Site(s):

This trial will be a single-center trial conducted in the United States.

Trial Device:

The device and system components used in this trial are shown below:

Cohort	System Component	Description
Cohort 1	MIT (placebo embedded with an IEM)	The MIT formulation is an IEM inside an inert tablet which will be dispensed to subjects to be ingested 15 times in 1 day during the trial.
Cohort 2	Abilify MyCite tablet (aripiprazole embedded with an IEM)	The Abilify MyCite formulation is an IEM inside an aripiprazole tablet which will be dispensed to subjects to be ingested one time during the trial.
Cohorts 1 and 2	D-Tect Patch	A D-Tect Patch will be applied by clinic staff prior to DOIs.
Cohorts 1 and 2	Computerized Device and Accessories	A computerized device (eg, smart phone) and accessories will be used by the clinic staff to track IEM detection on the software application.

DOI = directly observed ingestion; IEM = ingestible event marker; MIT = miniature ingestible event marker tablet.

Trial Assessments:

Assessments will include photographs of patches at application site, DOIs, Sleep Diary, and the Skin Irritation Scoring System (when applicable).

Independent Data Monitoring Committee: No

Statistical Methods:

The number of positive detection and PDA will be summarized for the D-Tect Patch for Cohort 1; the 95% confidence interval of PDA will be provided using the Clopper-Pearson method. A minimum of 24 subjects are planned to complete 15 DOIs per subject for Cohort 1. This will provide sufficient power to ensure the lower bound of the 95% confidence interval for PDA is at 95%, assuming the PDA rate of 97.3% of the D-Tect Patch using binomial distribution.

Summary statistics will be provided for Patch Detection Latency, Ingestion Data Transfer Latency, and Total Detection Latency. Kaplan-Meier curves will be plotted for all of the latency times.

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Trial Duration:

The total duration the subject is expected to be on trial is approximately 8 days and includes the following visits:

- Eligibility screening visit
- Testing Visit / Day 1 (1 day)
- Follow-up / Day 8 (1 day)

The trial start is defined as the date the first subject signs their informed consent form. Overall, the trial duration, from signing of the first subject's informed consent form to the last subject's final assessment, is expected to be approximately 24 days.

Known and Potential Risks and Benefits:

It is anticipated that subjects will be exposed to minimal risk during this trial. Subjects will wear patches and ingest IEMs. Subjects in Cohort 2 will ingest Abilify MyCite at the same dose as their currently prescribed aripiprazole. Subjects may experience adverse events (AEs) due to the digital medicine system including, but not limited to, skin irritation or allergic reaction. No direct subject benefit is expected by participation in this trial.

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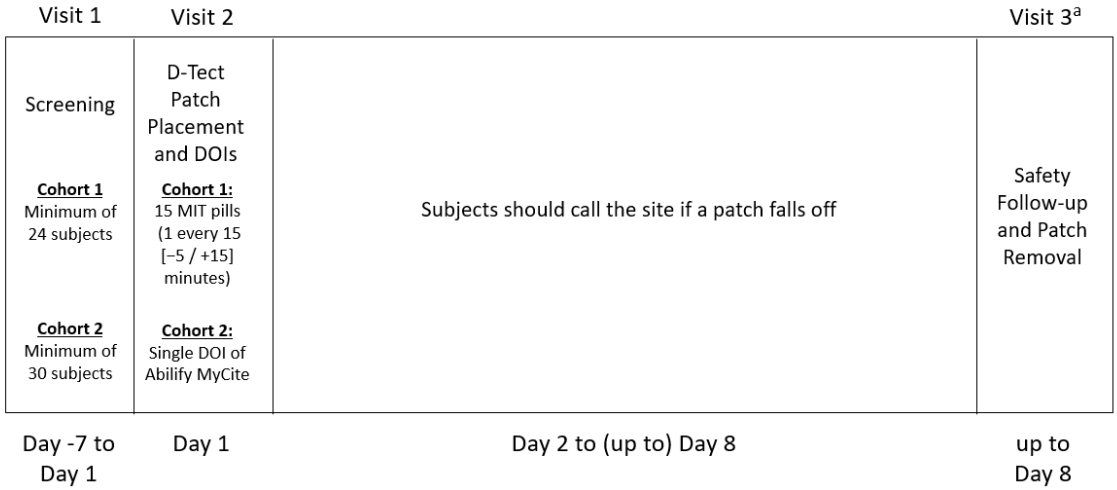
1.2 Schema



[a]If an in-person follow-up visit cannot occur due to severe acute respiratory syndrome coronavirus (SARS-CoV-2) restrictions (also known as coronavirus disease 2019 [COVID-19]), the site should conduct a follow-up video conference visit to verbally assess subject safety and instruct the subject to remove the patch at Day 8.

Figure 1.2-1 Trial Design Schematic (Cohorts 1 and 2)

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1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments (Cohorts 1 and 2)

Period	Screening	Testing	Follow-up
Visit	**Visit 1**	**Visit 2[a]**	**Visit 3[b,c]**
Trial Day	**Day −7 to Day 1**	**Day 1**	**Day 8 (+2 days)**
Informed Consent	X		
Demographics	X		
Medical History	X		
Concomitant Medications	X	X	X
Eligibility Criteria Review	X		
Vital Sign Measurements[d]	X		
Preparation of application site and patch placement		X	
Assessment of AEs[e]	X	X	X
Photograph of patches at application site[f]		X	X
DOI[g,h]		X	
Sleep Diary[i]		X	
Patch Removal[j]			X
Pregnancy Test[k]	X		

AE = adverse event; DOI = directly observed ingestion.

[a]Conducted either on the same day as Visit 1, or up to 7 days after Visit 1.

[b]In-person safety follow-up to occur 7 days after applying the patch.

[c]If an in-person follow-up visit cannot occur due to COVID-19 restrictions, the site should conduct a follow-up visit via video conference to verbally assess subject safety and instruct the subject to remove the patch on Day 8.

[d]Vital sign measurements include blood pressure, heart rate, temperature, height, and weight.

[e]If an AE is related to the patch, then the Skin Irritation Scoring System (Table 8.6.1-1) will be completed by the investigator.

[f]A minimum of 3 patch placement photos are required: prior to initial dose, after completion of DOI(s), and when the subject returns for follow-up (prior to patch removal).

[g]Cohort 1: Subjects will ingest 15 miniature ingestible event marker tablets (MITs) over the course of 1 visit day (with approximately 15 [−5 / +15] minutes between ingestions).

[h]Cohort 2: Subjects will ingest a single dose of Abilify MyCite at the same dose as their currently prescribed aripiprazole.

[i]On Day 1 of the trial, subjects will be sent home with a sleep diary to complete each day until they return for the follow-up visit on Day 8 [+ 2 days].

[j]Any patch that falls off during the trial should be retained by the subject and given to trial staff during the in-person follow-up visit. All patches must be removed on Day 8, even if the clinic visit is delayed.

[k]To be collected from woman of childbearing potential via urine dipstick.

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2 Introduction

The Digital Medicine System (DMS) has been designed to provide assistance with medication use and activities of daily living. The first DMS product (Abilify MyCite®) is approved by the United States Food and Drug Administration (FDA). When the ingestible event marker (IEM) is ingested, the DMS is intended to log, track, and trend intake times. When co-ingested with medication, the tracking and trending of intake times may be used as an aid to measure medication ingestion. Wearable sensors (WSs) or "patches" will be used to collect the raw signal data from the IEM. See Figure 2-1 for a visual of the DMS.

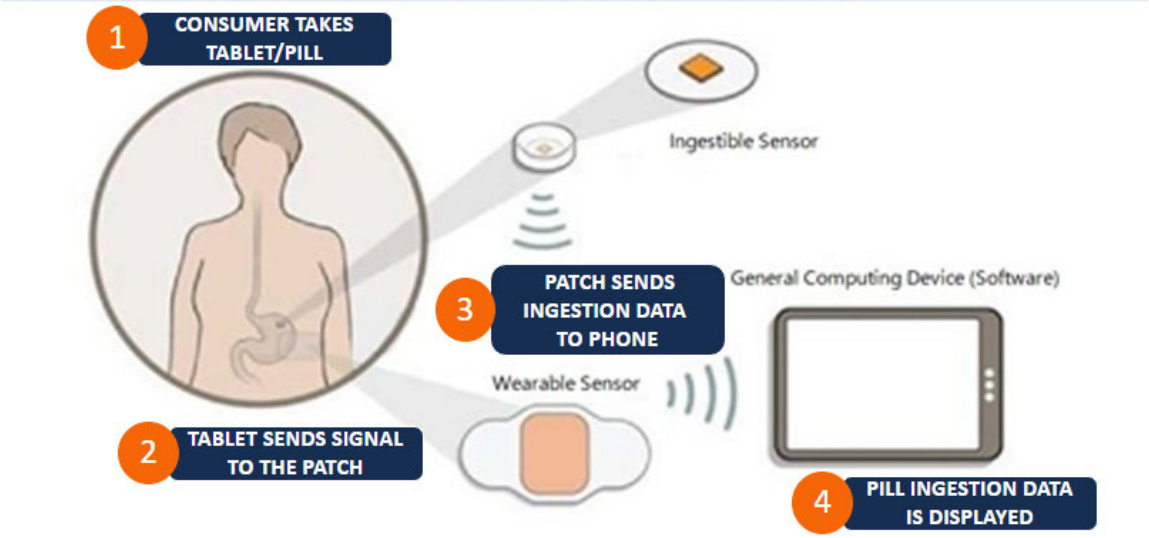

Figure 2-1 Digital Medicine System

Wearable Sensor

The WS that will be utilized in this testing is the D-Tect Patch. The D-Tect Patch is an unmedicated, battery-powered, adhesive-backed device that is worn on the torso (Figure 2-2). The WS contains electronic sensors capable of detecting the ingestion of the IEM and of measuring physiologic parameters. The WS automatically logs and stores the time when the IEM reaches the stomach and is activated and also automatically records and stores physiologic data and activities of daily living. Contact of the patch to the skin is made by conductive gel electrodes. Adequate quality of the patch-to-skin contact is assessed by determining an impedance value (in ohms) between the skin and the patch periodically (eg, every 20 minutes).

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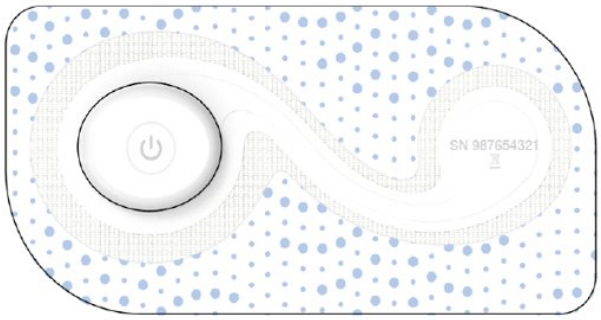

Figure 2-2 D-Tect Patch Design

In this trial, the D-Tect Patch should remain on the torso until removed by trial staff at the in-person follow-up visit. The patch placement zones are shown in Figure 8-1. Any patch that falls off during the trial must be retained by the subject and given to trial staff during the in-person follow-up visit.

Ingestible Event Marker

The IEM is a tiny device that is composed of a 1 mm x 1 mm x 0.3 mm silicon integrated circuit coated with thin layers of minerals and metals that rests in the center of an edible, cellulose-based disc. Within a few minutes after ingestion, the sensor uses the fluid in the stomach (pH independent) to provide the electrolyte for a biogalvanic battery formed by thin layers of the essential dietary minerals, magnesium, and copper deposited on the sensor's surface. The ensuing current is modulated by the IEMs microprocessor and creates an electric field that propagates through the body tissues to the skin surface. The modulated current is detected, decoded, recorded, and date- and time-stamped by the patch, which acts as a receiver. The IEM communicates with its identifier for a finite period of time of a few minutes and can be detected by the patch only when the patch is adherent to the subject's skin, thus providing personal privacy for data recording. This mimics the process whereby bioelectric signals from cardiomyocytes reach the electrodes of an electrocardiograph on the surface of the body. Each sensor's identifier is unique which makes it possible to differentiate multiple IEMs from one another when they are ingested at the same time. The IEM becomes inactive subsequently and is excreted in the feces. The IEM consists of tiny amounts of naturally occurring minerals found in the body and in food.

For this trial, testing will involve directly observed ingestions (DOIs) of the IEMs. Research staff will administer the IEMs to subjects and observe and record the time of each individual ingestion event.

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- For Cohort 1: The miniature IEM tablet (MIT) dose form will be used for testing. There are no active pharmaceutical ingredients in this dose form. Subjects will take 15 MITs over the course of 1 day, with approximately 15 (−5 / +15) minutes between ingestions.
- For Cohort 2: A single dose of Abilify MyCite (aripiprazole embedded with an IEM) will be used for testing. Abilify MyCite will be dispensed to subjects at the same dose as their current aripiprazole prescription. Abilify MyCite will be ingested at one time point during the trial.

Mobile Device with Mobile Application

The DMS also includes an application (app) software that is installed on a mobile device (eg, smartphone), which aggregates and displays the Otsuka WS data. The wireless Bluetooth-based interface within the WS is activated to transmit its stored encrypted data in a secure manner. The data transmitted by the WS include the IEM information, the WS serial number, impedance, and battery level and the physiologic parameters.

One mobile device will be provided to pair with the D-Tect Patch on the Testing Day during the DOI(s). All patches will be worn until the in-person follow-up visit. Software will be preloaded or loaded remotely (wirelessly) once testing has begun. Subjects will not be required to interact with the mobile device.

Please refer to the OPC-14597 Digital (Digital Medicine-Aripiprazole) Investigator's Brochure (IB) for more detailed information of the chemistry, pharmacology, efficacy, and safety of the DMS.

Detection Latency Metrics

There are 4 time-stamped events associated with measuring detection latency. These 4 events are shown in the system diagram in Figure 2-1 and further described below.

1) Subject takes tablet. Directly observed ingestion time is recorded by the clinician.
2) Tablet sends signal to the patch. Tablet is detected & recorded by the patch as an IEM record with a timestamp.
3) Patch sends ingestion data to phone. The tablet ingestion data is communicated to and recorded by the mobile device as a pill-ingestion-metric with a timestamp.
4) Tablet ingestion data is displayed. The tablet display event is triggered on the mobile device as a pill-display-event with a timestamp.

The latency between each of these timestamps is defined as:

- "Patch Detection Latency" is the time between steps 1) and 2)
- "Ingestion Data Transfer Latency" is the time between steps 2) and 4)
- "Total Detection Latency" is the total time between steps 1) to 4)

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2.1 Trial Rationale

This two-cohort, open-label, prospective trial is designed to assess the positive detection accuracy (PDA) and detection latency of the D-Tect Patch.

The PDA is defined as the proportion of MITs detected out of the total IEM detections of tested D-Tect Patches (Cohort 1 only).

For detection latency, Patch Detection Latency, Ingestion Data Transfer Latency, and Total Detection Latency will be measured for both cohorts (ie, MITs and Abilify MyCite). See Section 2 for the definition of the detection latency metrics.

2.2 Background

A new generation patch, the D-Tect Patch, has been developed for use in the DMS. The D-Tect Patch was designed to be thinner, more flexible, and contain less adhesive than predecessor patches. This trial is designed to collect the PDA (Cohort 1 only) and detection latency of the D-Tect Patch and involves 2 cohorts of subjects:

- Cohort 1 includes healthy subjects who will ingest MITs.
- Cohort 2 includes subjects with serious mental illness (SMI) (ie, Schizophrenia, Major Depressive Disorder, or Bipolar I Disorder) who are already prescribed and taking aripiprazole prior to trial entry. These subjects will ingest Abilify MyCite at the same dose as their currently prescribed aripiprazole.

2.3 Known and Potential Risks and Benefits

It is anticipated that subjects will be exposed to minimal risk during this trial. Subjects will be asked to wear a patch and ingest IEMs (MITs or Abilify MyCite). Subjects may experience adverse events (AEs) due to the DMS including, but not limited to, skin irritation or allergic reaction. No direct subject benefit is expected by participation in this trial.

The trial site will receive the IB, and the trial site should refer to the most current version as needed.

2.3.1 D-Tect Patch

2.3.1.1 Skin Irritation

Skin irritation may result from wearing the D-Tect Patch over the course of the wear period or from removing the patch.

2.3.1.2 Allergic Reaction

An allergic reaction could potentially arise from exposure to components of the patch adhesive.

To mitigate the risk of this potential hazard, prospective subjects who have a known allergy to skin adhesives will be excluded from the trial. Allergy to bandages, tapes, and latex will be specifically queried.

Subjects will be told that they are free to remove the patches at any time and to inform the clinical research site immediately. Subjects will also be told to reach out for emergency medical care should they have immediate need for medical attention.

2.3.2 Tablets

For Cohort 1, the MIT dose form does not contain active pharmaceutical ingredients.

For Cohort 2, subjects will ingest Abilify MyCite at the same dose as their currently prescribed aripiprazole. Abilify is contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients. Refer to the United States Prescribing Information (USPI) and Summary of Product Characteristics (SmPC) for complete warnings and precautions. All known drug interactions and other forms of interactions are described in the USPI and SmPC.

2.3.3 COVID-19 Management Plan

The clinical research site is expected to adhere to all United States Center for Disease Control (CDC), state, and local coronavirus disease 2019 (COVID-19) guidelines.

3 Objectives and Endpoints

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: • Evaluate PDA and detection latency measures for the D-Tect Patch.	PDA: Estimate PDA with the CI lower limit greater than 95% when a subject is wearing the D-Tect Patch. Detection Latency: The median Patch Detection Latency, Ingestion Data Transfer Latency, and Total Detection Latency. See Section 2 for the definition of the detection latency metrics.
Secondary: • To collect and characterize AEs associated with the device.	Safety: The frequency and severity of AEs, device-related AEs, serious AEs (SAEs), AEs leading to discontinuation, and unanticipated adverse device effects.

AE = adverse event; CI = confidence interval; PDA = Positive Detection Accuracy; SAE = serious adverse event.

Section 9.4 describes the statistical analysis of the endpoints.

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4 Trial Design

4.1 Type/Design of Trial

This two-cohort, open-label, prospective trial is designed to assess the PDA and detection latency of the D-Tect Patch.

Cohort 1

Cohort 1 will be completed in adult, healthy subjects. Subjects in Cohort 1 will take the MIT dose form. This trial will consist of up to 3 onsite visits including:

- Visit 1: Screening
- Visit 2 (Day 1): Testing, patch placement, DOI of MITs (conducted either on the same day as Visit 1 or up to 7 days after Visit 1)
- Visit 3 (Day 8): In-person safety follow-up and removal of patch (conducted approximately 7 days [+ 2 days] after applying the D-Tect Patch).

Cohort 2

Cohort 2 will be completed in adults with SMI who are prescribed and taking aripiprazole prior to trial entry. Subjects will take a single dose of Abilify MyCite at the same dose as subject's current aripiprazole prescription. Subjects will be instructed not to take their currently prescribed dose of aripiprazole at home on Day 1 of the trial when Abilify MyCite will be ingested. This trial will consist of up to 3 onsite visits including:

- Visit 1: Screening
- Visit 2 (Day 1): Testing, patch placement, DOI of a single dose of Abilify MyCite (conducted either on the same day as Visit 1 or up to 7 days after Visit 1)
- Visit 3 (Day 8): In-person safety follow-up and patch removal (approximately 7 days [+ 2 days] after applying the D-Tect Patch)

Cohorts 1 and 2

No trial procedures may be conducted prior to signing of the informed consent form (ICF), which will occur at Visit 1. Visit 2 involves patch application and DOI(s). Visits 1 and 2 may be combined and conducted on the same day. Subjects will return to the site on Day 8 (+ 2 days), 7 days following patch placement for a safety follow-up evaluation and to make final observations of patch wear (Visit 3). Any patches that remain on the subject will be removed at this visit. Any patch that falls off prior to the safety follow-up visit should be retained by the subject and given to trial staff at the scheduled follow-up visit.

A detailed schedule of events can be found in Table 1.3-1.

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4.2 Scientific Rationale for Trial Design

The D-Tect Patch is a new generation patch that has been developed for use in the DMS. Predecessor patches used in conjunction with the DMS were tested for packet detection performance as well as detection latency. This trial is being conducted to demonstrate that the D-Tect Patch performance is comparable to predecessor patch data.

4.3 Dosing Rationale

In Cohort 1, no medication will be ingested.

In Cohort 2, subjects will ingest a single dose of Abilify MyCite (aripiprazole embedded with an IEM) at the same dose as their currently prescribed aripiprazole. The following doses of Abilify MyCite are available for use in this trial: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg. The dose of Abilify MyCite will be recorded in subject's source documentation and the electronic case report form (eCRF).

4.4 Start and End-of-Trial Definitions

The trial start is defined as the first visit of the first subject, which is the date the first subject signs their ICF.

The end-of-trial date is defined as the last date of contact, or the date of final contact attempt as recorded in subject's source documentation for the last subject completing or withdrawing from the trial.

4.5 Definition of Completed Subjects

The trial period is defined as the time period during which subjects are evaluated for the primary objective of the trial irrespective of whether or not the subject wears the patch or ingests all IEMs. Subjects who are evaluated at the last scheduled visit will be defined as trial completers.

5 Trial Population

Two cohorts of subjects will be enrolled in this trial.

Cohort 1: A minimum of 24 healthy subjects will be tested to obtain a minimum of 360 miniature IEM tablet ingestions for Cohort 1. Healthy subjects will be drawn from nonvulnerable subpopulations. If a subject fails to complete participation in the testing, for whatever reason, a new, qualified candidate may be enrolled as a replacement.

Cohort 2: A minimum of 30 subjects with SMI will be tested to obtain a minimum of 30 Abilify MyCite ingestions for Cohort 2. Subjects will ingest Abilify MyCite at the same dose as their currently prescribed aripiprazole. If a subject fails to complete

participation in the testing, for whatever reason, a new, qualified candidate may be enrolled as a replacement.

5.1 Subject Selection and Numbering

All subjects will be given a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits] upon providing consent). The site number will be designated by the sponsor. The subject number will be given sequentially from S00001.

Demographic information (date of birth, sex at birth, gender identification, childbearing potential, race, ethnicity) and medical history will be recorded in the eCRF at the screening visit.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the sponsor.

5.2.1 Inclusion Criteria

Subjects are required to meet the inclusion criteria shown in Table 5.2.1-1 to participate in Cohort 1 of the trial:

Table 5.2.1-1 Inclusion Criteria (Cohort 1)

1.	Have read, reviewed with trial site staff, and signed the informed consent.
2.	Male or female at least 18 years of age.
3.	In good general health or medically stable.
4.	Is able and willing to participate in, and adhere to, all testing procedures, both onsite and offsite, for the entire testing.
5.	Subject has access to a telephone for communicating with the trial personnel and for trial personnel to contact the subject.

Subjects are required to meet the inclusion criteria shown in Table 5.2.1-2 to participate in Cohort 2 of the trial:

Table 5.2.1-2 Inclusion Criteria (Cohort 2)

1.	Have read, reviewed with trial site staff, and signed the informed consent.
2.	Male or female at least 18 years of age.
3.	In good general health or medically stable.
4.	Has confirmed diagnosis of Schizophrenia, Major Depressive Disorder, or Bipolar I Disorder per Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-5) criteria and currently prescribed and taking aripiprazole.
5.	Is able and willing to participate in, and adhere to, all testing procedures, both onsite and offsite, for the entire testing.
6.	Subject has access to a telephone for communicating with the trial personnel and for trial personnel to contact the subject.

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5.2.2 Exclusion Criteria

Subjects will be excluded from Cohort 1 and/or Cohort 2 if they meet any of the exclusion criteria shown in Table 5.2.2-1:

Table 5.2.2-1 Exclusion Criteria (Cohort 1 and Cohort 2)

1.	Any medical condition, treatment, or symptoms that, in the judgment of the trial clinician, could place the subject at more than the minimal risk from involvement in the testing.
2.	Hospitalization, emergency room visit, surgery or new medical treatment within 30 days before testing begins or planned during testing.
3.	Difficulty with or inability to swallow tablets.
4.	Active skin infection or active dermatitis, OR history of chronic inflammatory skin condition including psoriasis and chronic dermatitis (except atopic dermatitis).
5.	The investigator will determine if any subject should be excluded from the trial based on history of, OR current, alcohol abuse, drug abuse or use of illegal drugs (eg, amphetamines or heroin).
6.	Allergy to adhesive bandages/tapes (eg, Band-Aids®) or latex.
7.	Positive urine pregnancy test at screening visit (dipstick).
8.	Subject is taking any concomitant medication that places the subject at a greater risk for skin reactions or skin sensitivity.

A definition of childbearing potential can be found in Section 10.2.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who does not have a patch applied. All AEs must be reported after subject informed consent has been obtained, including screen failures due to AEs, irrespective of trial intervention administration.

If the subject meets the definition of a screen failure in this trial, the following information will be recorded in the eCRF:

- Date of ICF signature
- Visit date (screening visit)
- Demographics
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure
- Any AEs

Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened.

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6 Trial Device(s) and Concomitant Therapy

6.1 Trial Device(s) Administered

Trial devices intended to be administered to the subjects during the conduct of the trial are listed in Table 6.1.1-1.

For information regarding the dose and observation period(s), including any follow-up period for the trial, see Section 4.1.

6.1.1 Medical Devices

The system components used in this trial are shown below in Table 6.1.1-1.

Table 6.1.1-1 System Components to be Tested

Cohort	System Component	Description
Cohort 1	MIT (placebo embedded with an IEM)	The MIT formulation is an IEM inside an inert tablet which will be dispensed to subjects to be ingested 15 times in 1 day during the trial.
Cohort 2	Abilify MyCite tablet (aripiprazole embedded with an IEM)	The Abilify MyCite formulation is an IEM inside an aripiprazole tablet which will be dispensed to subjects to be ingested one time during the trial.
Cohorts 1 and 2	D-Tect Patch	A D-Tect Patch will be applied by clinic staff prior to DOIs.
Cohorts 1 and 2	Computerized Device and Accessories	A computerized device (eg, smart phone) and accessories will be used by the clinic staff to track IEM detection on the software application.

6.2 Management of Trial Device

For full details on management of trial device(s), please refer to the trial-specific operations manual.

6.2.1 Packaging and Labeling

The D-Tect Patches will be provided by the sponsor or designated agent to the site. The D-Tect Patches will be supplied in pouches. Each patch used will be labeled to clearly disclose the unique patch serial number (SN) and lot number. The SN and lot number will be recorded in the eCRF.

The IEMs (MITs and Abilify MyCite) will be provided by the sponsor or designated agent to the investigators and the persons designated by the investigator(s) or institution(s). The MITs and Abilify MyCite will be supplied in bottles. For Abilify MyCite, 1 bottle of each dose will be supplied to the site.

6.2.2 Storage

The device and components (ie, patches and IEMs [MITs and Abilify MyCite]) will be stored in a securely locked cabinet or enclosure. MITs and Abilify MyCite must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of the D-Tect Patches, IEMs (MITs and Abilify MyCite), and mobile device(s) received, dispensed, administered, returned, and lost (if applicable). Neither the investigator nor any designees may provide a device to any subject not participating in this trial.

6.2.4 Returns and Destruction

The mobile devices will be returned to the sponsor representatives after completion of all ingestions on Day 1.

The D-Tect Patches will be collected by the sponsor representatives after accountability. Upon completion or termination of the trial, all used and unused D-Tect Patches must be returned to the sponsor or a designated agent. All D-Tect Patches returned to the sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned D-Tect Patches should be in the original containers and used patches should be stuck to the inside of a zip lock bag. The assigned trial monitor will facilitate the return of used and unused D-Tect Patches.

Tablets (MITs and/or Abilify MyCite) may be returned to the sponsor and/or destroyed by the clinical trial site following completion and verification of accountability. Refer to the Pharmacy Manual for instructions on returns and/or destruction.

6.2.5 Reporting of Product Quality Complaints

Product Quality Complaints (PQCs) will be reported for Abilify MyCite tablets only. PQCs will not be reported for the D-Tect Prototype Patch, MIT dose form, or app.

A PQC is any written, electronic, or oral communication provided by a healthcare professional, consumer, clinical trial subject, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device or

medicinal product or a falsified, tampered, or diverted product after it is released for distribution.

Examples include, but are not limited to, communications involving:

- Failure of a product to meet any of its specifications.
- Incorrect or missing labeling.
- Packaging issues: (eg, damaged, dirty, crushed, missing tablet, missing patch/pod, missing component).
- Tablet/bottle defects: (eg, odor, under-filled bottle, empty bottle, over-filled bottle, tablet not registering with the app, chipped tablet, broken tablet).
- Loss or theft of product.

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record each PQC identified through any means from the receipt of the Abilify MyCite tablets from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) within 24 hours of becoming aware of the PQC according to the procedure outlined below.

Send PQC reporting information to the OPDC IMP complaints mailbox email:

Email: IMP-PQC@otsuka-us.com

Also indicate whether or not the complaint sample is available for return.

Identification of a PQC by the subject should be reported to the site investigator, who should then follow the reporting mechanism above.

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, subject, investigator, site, etc)
- Reporter contact information (eg, address, phone number, email address)
- Subject number
- Clinical site number
- ID of material (product/compound name, lot/batch number, shipment number, expiry date)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return.

If the complaint sample is available for return, the return instructions will be provided by the sponsor.

It must be documented in the site accountability record that the complaint sample has been forwarded to the sponsor for complaint investigation.

6.2.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

6.3 Measures to Minimize/Avoid Bias

This is an open-label trial.

6.4 Subject Compliance

A subject will be withdrawn from the trial by the investigator (or designee) if the subject is noncompliant with the protocol (defined as refusal or inability to adhere to the trial schedule or procedures) and the details will be recorded on the appropriate eCRF.

6.5 Dose Modification

Not applicable. Subjects in Cohort 2 will be administered a single dose of Abilify MyCite at the same dose as their currently prescribed aripiprazole dose.

6.6 Prior/Concomitant Medications or Therapies

The investigator will record all medications (including, but not limited to, prescription medications, over-the-counter medications, vitamins, herbal remedies, etc) and therapies taken by the subject from 7 days prior to D-Tect Patch application through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) in the eCRF. The investigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the eCRF.

6.7 Intervention After the End of the Trial

Not applicable.

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7 Discontinuation of Trial/Treatment and Subject Discontinuation/Withdrawal

7.1 Entire Trial or Treatment

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

7.2 Individual Site Discontinuation

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

7.3 Discontinuation of Trial Device

Under certain circumstances, it may be necessary for a subject to permanently discontinue the trial. If trial IEMs or patches are permanently discontinued, the subject should, if at all possible, remain in the trial to be evaluated for safety assessments. See the schedule of assessments (SoA) for data to be collected at the time of discontinuation of trial device and follow-up and for any further evaluations that need to be completed. If a subject discontinues the trial due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

For each subject who discontinues the trial, the main reason for discontinuation will be recorded in the eCRF (refer to Section 7.4.1).

7.3.1 Interruption of Trial Procedures

If a subject temporarily interrupts trial device use due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. For each subject who has an interruption in trial device use, the main reason for interruption will be recorded in the eCRF.

7.4 Subject Discontinuation/Withdrawal from the Trial

- A subject may withdraw from the trial at any time at the subject's own request for any reason (or without providing any reason).
- A subject may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

- At the time of discontinuing from the trial, if possible, an early discontinuation visit should be conducted to assess any new or ongoing AEs.
- If a subject withdraws consent from the trial, the subject will be permanently discontinued from all trial procedures and the trial.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before the withdrawal of consent.

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

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial site staff).
- Contact of the subject by trial site staff, even if only by telephone, to assess current medical condition, and obtain necessary medical reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or email (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.4.1 Documenting Reasons for Subject Discontinuation/Withdrawal

A subject may discontinue the trial or withdraw from the trial for the reasons listed below:

- Adverse event
  - Continuing investigational device and/or ingestion of IEMs (MITs and/or Abilify MyCite) places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to the investigational device or its components)
  - Serious adverse event (SAE)
  - Other potentially investigational device-related safety concerns or AEs

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- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Protocol-specific withdrawal criterion met
- Site terminated by sponsor
- Withdrawal by subject

7.5 Lost to Follow-up

Subjects who cannot be contacted on or before Visit 3 (Day 8 [+ 2 days]) during the trial period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up."

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

If the subject was classified as "lost to follow-up," the following information will be recorded in the eCRF: "Date of final contact attempt" and "Contact method."

8 Trial Procedures

This trial consists of up to 3 days of onsite testing activities, including the screening visit, testing visit (conducted either on the same day as Visit 1 or up to 7 days after Visit 1), and the in-person safety follow-up visit, which will occur on Day 8 (+ 2 days). The D-Tect Patch will be worn until the in-person follow-up visit. Consent will be obtained from subjects prior to conduct of any testing related assessments or procedures in a manner consistent with GCP.

The assessments to be conducted during the trial are summarized in Table 1.3-1.

Screening

The informed consent process will be administered at Visit 1. The investigator (or designee) will determine whether a subject meets all eligibility criteria. In addition to gathering information specifically pertaining to the eligibility criteria, the investigator (or designee) will conduct a brief health screen. Only responses related to the eligibility criteria will be recorded in the eCRF. The investigator (or designee) will include this assessment in determining whether the level of risk for an individual is acceptable for

participating in testing and will record whether the risk is acceptable on the appropriate screening eCRF. All recorded information will be de-identified. A physical examination is not required to be performed as part of screening, although evaluation of any subsequent AEs may require a targeted exam by a member of the clinical staff. Subjects will be instructed not to take their prescribed dose of aripiprazole on Day 1 of the trial.

Testing Visit

The research staff will meet with subjects for activities specified in Table 1.3-1 including assessment of AEs, review of concomitant medications, preparation of skin for patch placement, patch placement and photographs, DOI(s), and administration of the Sleep Diary. Subjects' food and drink intake on the Testing Day will be recorded by clinic staff.

Trained research staff will prepare subject skin to ensure good patch adhesion and place the D-Tect Patch on the subject. Skin preparation techniques may include cleansing of the skin with the provided "Simple" brand wipes, and/or clipping or shaving of excessive hair. To place the D-Tect Patch, the subject will be required to temporarily shift their shirt (and undergarments, if applicable) to allow access to the upper body. Even numbered subjects will have one D-Tect Patch placed on the right costal margin, anywhere from the xiphoid to the right mid-axillary line. Odd numbered subjects will have one D-Tect Patch on the left costal margin, anywhere from the xiphoid to the left mid-axillary line as shown in Figure 8-1.

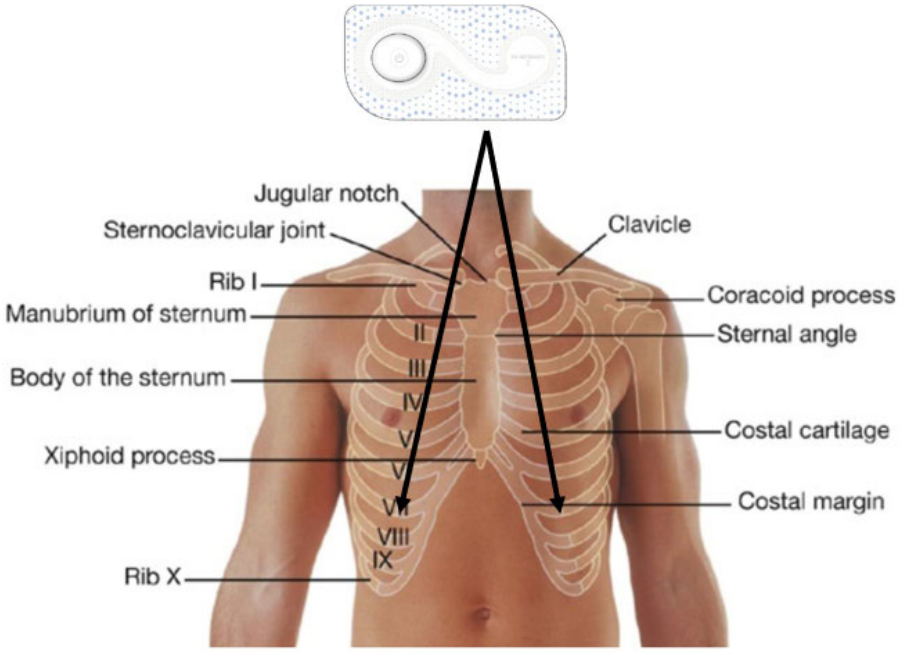

Figure 8-1 Wearable Sensor Placement Zones

After the D-Tect Patch is successfully placed, the subject can readjust their clothes. Staff will confirm that no patch placed comes into contact with the wire within a bra (where applicable). Non-site trial staff may perform quality control (QC) of patch placement on subjects. Patch placement photographic evidence will be documented. A minimum of 3 patch placement photos is required:

1) Prior to initial dose
2) After completion of the 15th MIT dose (Cohort 1) or after completion of the single dose of Abilify MyCite (Cohort 2)
3) When the subject returns for follow-up prior to removing the patch

One day of DOIs is planned for this trial. Subjects will ingest tablets per the dosing outlined in Table 8-1 below. For subjects in Cohort 2, site staff will confirm that subjects did not take their prescribed dose of aripiprazole at home prior to the DOI of Abilify MyCite. Subjects will ingest tablets with approximately 60 mL of bottled water. The tablets will be administered by research staff and staff members will observe and record the timing of the individual ingestion events on the DOI eCRF. Site staff will conduct mouth checks and also verify cheeking after a subject swallows each tablet.

Table 8-1 Dosing Schedule

Cohort	Ingestions/Session	Time Between Dosing Sessions (minutes)	Visit
Cohort 1	One IEM tablet (MIT dose form) / 15 times	Approximately every 15 (−5 / +15) minutes	2
Cohort 2	Single dose of Abilify MyCite / 1 time	Not applicable	2

For any subject where tablet registration is missing, the trial team will consider execution of additional trial parameters including, but not limited to the following: ruling out bad patch impedance (eg, patch is not adhering to the skin properly) that can be addressed by changing the patch, potential contamination of the placebo tablets by introducing a new, sealed bottle of placebo tablets, and removing the DMS from the patient and having a non-site related, sponsor representative test the system independent of the subject to rule out unexplained subject anomalies (eg, medical or unknown conditions that may prevent patch registration of the ingested tablet). Any parameters executed may necessitate additional subject enrollment to replace missing ingestions during trial testing.

Subjects will be sent home with a Sleep Diary to complete each day until they return for the follow-up visit on Day 8 [+ 2 days]. Instructions on how to complete the sleep diary will be provided to the subject by the trial staff.

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Follow-up Visit

All patches will be removed by trial staff at the in-person follow-up visit if the patch is still adhered on Day 8 [+ 2 days]. Any patch that peels off during the trial should be retained by the subject and given to trial staff during the scheduled in-person follow-up visit. If an in-person follow-up visit cannot occur, the site should conduct a telephone follow-up visit to assess safety and instruct the subject to remove the patch on Day 8. If the in-person follow-up visit is delayed past Day 8, subjects should be instructed to remove the patch on Day 8 and retain the patch to be given to site staff the in-person follow-up visit.

Subjects will return the completed Sleep Diary to trial staff at this visit.

At the in-person safety follow-up visit, information regarding AEs that may have occurred during or since Visit 2 will be elicited. Any ongoing AE associated with the use of the device or IEMs at the in-person follow-up visit should be followed to resolution per the judgment of the investigator unless the subject is lost to follow-up. If an in-person follow-up visit cannot occur, the site should conduct a telephone follow-up visit and verbally assess subject safety.

Responsibilities for Testing Subjects

- Wear the D-Tect Patch on the torso during the Testing Day and leave the patch on the torso until the in-person follow-up visit or the patch falls off.
- Complete a Sleep Diary each day until the in-person follow-up visit.
- Direct observed ingestions:
  - Cohort 1: Swallow 15 MITs in a single calendar day.
  - Cohort 2: Swallow a single dose of Abilify MyCite in a single calendar day at the same dose as subject's aripiprazole prescription.
- Subjects must be comfortable reporting any AEs (Section 8.7).
- Participate in all onsite visits and procedures.
- Participate in an in-person safety follow-up site visit approximately 7 days (+ 2 days) after applying the D-Tect Patch. All patches will remain on the torso until removed by trial staff at the in-person follow-up visit on Day 8. If a patch falls of early, the subject should retain the patch and return it to site staff at their scheduled in-person follow-up visit.

8.1 Efficacy Assessments

Not applicable.

8.2 Pharmacokinetic Assessments

Not applicable.

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8.3 Biomarker Assessments

8.3.1 Pharmacodynamic Assessments

Not applicable.

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Future Biospecimen Research Samples

Not applicable.

8.6 Safety Assessments

Reporting of AEs associated with the use of the device or ingestion of IEMs (MITs or Abilify MyCite) will occur during active testing participation. AEs will be triaged and assessed as appropriate (Section 8.7).

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.7.

8.6.1 Skin Irritation Scoring System

If an AE is related to the patch, then the Skin Irritation Scoring System (Table 8.6.1-1) will be completed by the investigator.[1] A photo of the affected area should also be taken. Patch-related AEs Grade 2 or above will be considered clinically significant for purposes of this trial and must be recorded on the safety reporting form and on the eCRF.

Table 8.6.1-1 Skin Irritation Scoring System

Grade	Skin Event
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond the test site

Source: United States (US) Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, December 1999.[1]

8.6.2 Clinical Laboratory Assessments

Not applicable.

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8.6.3 Physical Examination

A physical examination is not required to be performed as part of screening, although evaluation of any subsequent AEs may require a targeted exam by a member of the clinical staff.

8.6.4 Vital Signs

Vital signs will be collected at the time point described in the schedule of assessments (Section 1.3). Subject vital signs should be monitored and assessed for potential clinical significance.

8.6.5 Electrocardiogram

Not applicable.

8.7 Adverse Events

8.7.1 Definitions

- Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or IEMs (MITs and/or Abilify MyCite) and whether anticipated or unanticipated.[2]
- Serious adverse event (SAE): AE that led to any of the following:
  - Death
  - Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    - A life-threatening illness or injury
    - A permanent impairment of a body structure or a body function including chronic diseases
    - Inpatient or prolonged hospitalization
      - Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered an SAE
    - Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function
  - Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment
  - Nonserious AEs: all AEs that do not meet the definition of an SAE are considered nonserious AEs.
- Immediately Reportable Event (IRE):
  - Any SAE.

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

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

Causality: Assessment of causal relationship of an AE to the use of the patch, MITs, and/or Abilify MyCite is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the patch, MITs, and/or Abilify MyCite and the AE.
Not Related:	There is no temporal or causal relationship between the patch, MITs, and/or Abilify MyCite and the AE.

8.7.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs (serious and nonserious, associated with the use of the patch, MITs, and/or Abilify MyCite) from the time the ICF is signed until the end of the trial. For this trial, information on AEs will be followed until resolution as determined by the investigator. All patches will be removed by trial staff at the in-person follow-up visit. Any patch that peels off during the trial should be retained by the subject and given to trial staff at the scheduled in-person follow-up visit.

To avoid bias in eliciting AEs, subjects should be asked the nonleading question: “How have you felt since your last visit?” All AEs (serious and nonserious) must be collected. All SAEs must be reported within 24 hours of awareness, no later than 72 hours in the case of a weekend or holiday. If a patch-related AE is reported by the subject, it will be graded per Section 8.6.1. A full list of all reported events will be kept by the clinical research site.

For this trial, all IREs (SAEs) detected during the program must be reported to:

- Global_intake@otsuka-us.com
- (fax) 301-212-8626

Reconciliation of AEs reported in this trial will be performed at the end of the trial.

8.7.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after he/she or site personnel become aware of any IRE (SAE), by telephone, fax, or e-mail to

the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Patient confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.7.7.2.

8.7.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.7.5 Adverse Events of Special Interest

Not applicable.

8.7.6 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.7.7 Follow-up of Adverse Events

8.7.7.1 Follow-up of Nonserious Adverse Events

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

8.7.7.2 Follow-up of Immediately Reportable Events and Serious Adverse Events

This trial requires that subjects be actively monitored for IREs (SAEs) up to 7 days (+2 days) after applying the D-Tect Patch and DOIs.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to the last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.7.3.

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

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

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

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

Any new IREs (SAEs) reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the trial intervention(s), should be reported to the sponsor according to the procedures outlined in Section 8.7.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. Any significant follow-up information should continue to be reported to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.8 Treatment of Overdose

For this trial, any dose of Abilify MyCite that is greater than the planned dose level (ie, subjects are planned to ingest Abilify MyCite at the same dose as their currently prescribed aripiprazole) will be considered an overdose for Cohort 2. In the event of an overdose, refer to the Abilify MyCite USPI for management of overdosage. To mitigate the risk of potential overdose, site staff will confirm that subjects do not take their prescribed dose of aripiprazole at home prior to the DOI of Abilify MyCite.

8.9 Subject Assessment Recording

Not applicable.

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8.10 Other Assessments

8.10.1 Positive Detection Accuracy

The number of total DOIs will be reported by the site on the eCRF. Positive detections will be downloaded from the trial mobile device(s) for analysis.

8.10.2 Detection Latency Measures

The DOI time will be recorded in the eCRF to the nearest minute by the site. Signal detection times will be downloaded from the trial mobile device(s) for analysis.

8.10.3 Sleep Diary

On Day 1 of the trial, subjects will be sent home with a sleep diary to complete each day until they return for the follow-up visit on Day 8 [+ 2 days]. Instructions on how to complete the sleep diary will be provided to the subject by the trial staff. The sleep diary responses will be reported by the site on the eCRF.

9 Statistical Considerations

9.1 Sample Size

For Cohort 1, a minimum of 24 subjects are planned to complete 15 DOIs per subject. With this assumption, 24 subjects with 360 ingestions will provide sufficient power to ensure the lower bound of the 95% confidence interval (CI) for PDA is at 95% assuming the PDA rate of 97.3% of the D-Tect Patch using binomial distribution.

For Cohort 2, there is no formal sample size calculation. A minimum of 30 subjects are planned to complete a single DOI of Abilify MyCite.

9.2 Datasets for Analysis

The following analysis samples are defined for this trial:

- Enrolled Sample: all subjects who sign an ICF and enter the trial (and only subjects who meet all the inclusion criteria and none of the exclusion criteria).
- The intent-to-treat (ITT) population: ITT population consists of all subjects who took at least 1 dose of MITs or Abilify MyCite.
- Safety Sample: all subjects who wear any patch or take any tablet from the trial and have any safety assessment.

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

Missing data on PDA and/or detection latency measures will not be imputed.

9.4 Statistical Analyses

9.4.1 Primary Endpoints

The number of positive detections and PDA will be summarized for the D-Tect Patch for Cohort 1; the 95% CI of PDA will be provided using the Clopper-Pearson method. PDA is defined as PDA = $k \div n$, where n is the number of the total DOIs, and k is the number of positive detections by the patch.

For detection latency, summary statistics will be provided for Patch Detection Latency, Ingestion Data Transfer Latency, and Total Detection Latency. Kaplan-Meier curves will be plotted for all of the latency times.

9.4.2 Secondary Endpoint

The frequency and severity of AEs, device-related AEs, SAEs, AEs leading to discontinuation, and unanticipated adverse device effects will be summarized.

9.4.2.1 Adverse Events

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

- AEs
- AEs by severity
- AEs potentially causally related to the investigational device
- AEs with an outcome of death
- SAEs
- AEs leading to discontinuation of the investigational device

9.4.2.2 Clinical Laboratory Data

Not applicable.

9.4.2.3 Physical Examination and Vital Signs Data

Baseline vital signs data will be provided in a listing.

9.4.2.4 Electrocardiogram Data

Not applicable.

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9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, sex at birth, gender, etc, will be summarized by cohort using descriptive statistics. Summary statistics will consist of mean, median, minimum, maximum, and standard deviation for continuous variables and tabulations of frequency distributions for categorical variables.

9.5 Interim Analysis

No interim analysis or adaptive design are applicable.

10 Supporting Documentation and Operational Considerations

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

10.1.1 Ethics and Responsibility

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

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

10.1.2 Informed Consent

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

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

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

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

Once appropriate essential information has been provided and fully explained in layman’s language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions and have those questions answered, the IRB-approved paper ICF will be signed and dated by both the

subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

10.1.3 Recruitment Strategy

Subjects may be recruited through several sources, including but not limited to the site database and advertising in traditional or online media.

10.1.4 Confidentiality

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

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

10.1.5 Quality Control and Quality Assurance

10.1.5.1 Monitoring

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

10.1.5.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, investigational device supply, presence of required documents, the informed consent process, site operations, delegation of authority and training, and a review of the eCRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

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

10.1.6 Protocol Deviations

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

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

10.1.7 Records Management

10.1.7.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, progress notes, paper-based assessments and scales, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

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

10.1.7.2 Data Collection

During each subject's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised ICFs;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to initiation of any trial procedures, and confirmation of the subject's actual participation in the trial;
- Documentation of baseline and demographic characteristics (eg, age, sex at birth, race, ethnicity);
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to trial investigational device must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and trial procedure compliance;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC) system that is 21 Code of Federal Regulations (CFR) Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

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

10.1.7.3 File Management at the Trial Site

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

10.1.7.4 Records Retention at the Trial Site

The FDA regulations require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

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

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

10.1.7.5 Dissemination of Clinical Trial Data

Not applicable.

10.1.7.6 Publication Authorship Requirements

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

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

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

Investigators or other personnel involved in the conduct of the trial who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing

to participate in the trial, investigators or other personnel involved in the conduct of the trial consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential (FOCBP) are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months). Females of non-childbearing potential do not meet definition of FOCBP.

Any subject that is currently pregnant or planning to become pregnant at the time of trial start is not eligible for participation. Females of childbearing potential are required to have a negative urine pregnancy test during screening. Subjects prescribed and taking aripiprazole should consult with their prescribing physicians regarding contraceptive recommendations with respect to family planning.

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10.3 Appendix 3: Protocol Amendments

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

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

10.3.1 Protocol Amendment(s)

Not applicable.

11 References

1 US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, December 1999.

2 International Organization for Standardization. ISO 14155:2020(en): Clinical investigation of medical devices for human subjects - Good clinical practice. August 2020.

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Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational device, D-Tect Patch and ingestible event markers, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where the D-Tect Patch and ingestible event markers will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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SIGNATURE PAGE

Document Name: 031-201-00521_Protocol

Document Number: CCI [redacted]

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