

Official Title: A Phase IIIb Multi-Center, Open-Label, Mirror-Image, Trial in Adult Subjects With Schizophrenia Treated Prospectively for 6-months With Abilify MyCite®

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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Aripiprazole Digital (OPC-14597-Digital)

REVISED CLINICAL PROTOCOL

A Phase IIIb Multi-Center, Open-Label, Mirror-Image, Trial in Adult Subjects with
Schizophrenia Treated Prospectively for 6-months with Abilify MyCite®

Protocol No. 031-201-00301

IND No. 115927

CONFIDENTIAL – PROPRIETARY INFORMATION

Drug Development Phase:	3b
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Aripiprazole Digital (OPC-14597-Digital)	Protocol No.: 031-201-00301 IND No.: 115927
Protocol Title:	A Phase IIIb Multi-Center, Open-Label, Mirror-Image, Trial in Adult Subjects with Schizophrenia Treated Prospectively for 6-months with Abilify MyCite [®]
Clinical Phase:	3b
Treatment Indication:	Schizophrenia
Objective(s):	<p>Primary:</p> <ul style="list-style-type: none"> • To compare inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalizations) between the retrospective period (Months 1 to 3) while subjects are on oral standard-of-care antipsychotic treatment and the prospective period (Months 1 to 3) after the subjects switch to Abilify MyCite. <p>Secondary:</p> <ul style="list-style-type: none"> • To evaluate improved adherence of Abilify MyCite based on overall proportion of days covered (PDC). • To further evaluate long-term safety and tolerability of Abilify MyCite.
Trial Design:	<p>This is a phase 3b, open-label, prospective, clinical trial designed to assess the difference between inpatient psychiatric hospitalization rates in subjects on oral standard-of-care antipsychotic treatment(s) for a period of 6 months followed by a switch to Abilify MyCite for a period of 3 months (Months 1 to 3). At the Month 3 visit, the investigator should decide if subjects will continue on Abilify MyCite for an additional 3 months (Months 4 to 6) or switch to a standard-of-care treatment (eg, oral atypical antipsychotics or a long acting injectable [LAI]) for the duration of treatment.</p> <p>This trial will include male and female subjects who are 18 to 65 years of age, inclusive, with a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Subjects must have had at least 1 inpatient psychiatric hospitalization within 4 years (48 months) and must have been prescribed oral</p>

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antipsychotics for at least 6 months or longer prior to screening.

Subjects will enter a screening period (up to 45 days). If deemed eligible to participate, subjects will enter an open-label Abilify MyCite treatment prospective phase for up to 6 months.

Oral Standard-of-Care Antipsychotic Treatment(s)
(Retrospective Phase)

To be eligible for trial participation, subjects must have been prescribed oral antipsychotic standard-of-care pharmacotherapy for at least 6 months or longer, with evidence of prescription (ie, pharmacy records) during the retrospective phase and prior to screening. Subjects administered antipsychotics other than aripiprazole must cross-titrate onto oral aripiprazole during the screening period at the discretion of the investigator to be eligible for trial participation.

Screening

After providing informed consent, subjects will enter the 45-day (Days -45 to -1; approximately 6 weeks) screening period to determine if they are eligible to enter the Abilify MyCite treatment (prospective) phase. The subject's past psychiatric history for the 6 months prior to screening must be available, inclusive of a comprehensive review of all psychiatric hospitalizations and interventions (psychiatric only).

Subjects who meet the inclusion/exclusion criteria and who are receiving antipsychotic medication(s) other than aripiprazole and who have no history of tolerating oral aripiprazole may be converted to oral aripiprazole monotherapy through cross-titration and undergo an assessment of aripiprazole tolerability at the discretion of the investigator. Subjects currently receiving oral aripiprazole monotherapy, or subjects currently taking any antipsychotic other than oral aripiprazole and have a history of tolerating oral aripiprazole may enter the Abilify MyCite treatment phase directly as long as the investigator deems subject safety is maintained and adequate psychiatric records are documented.

Abilify MyCite Treatment (Prospective) Phase

For subjects enrolled in the trial, those not on aripiprazole at screening and who need to cross-titrate will do so during the screening period for conversion to aripiprazole from other

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antipsychotics according to the approved labels. At the baseline visit (Day 1), Abilify MyCite onboarding will be provided with informational materials and additional call center support. Initiation of Abilify MyCite treatment will commence at the baseline (Day 1) visit, with subjects ingesting the Abilify MyCite tablet embedded with an ingestible event marker (IEM) sensor product, wearing the patch, and using the smartphone app for up to 6 months, including a required 3 months (Months 1 to 3) of Abilify MyCite treatment. This will be followed, at investigator discretion, to either change to standard-of-care antipsychotic treatment (eg, oral or LAI) or remain on Abilify MyCite for the second 3-month period (Months 4 to 6) during the prospective phase. The first dose of Abilify MyCite is to be taken at the baseline (Day 1) visit (in the clinic) during onboarding, unless subjects have already taken their daily dose. Subjects should not take their oral standard-of-care medication that morning before the baseline (Day 1) visit.

During the assessment period, subjects will visit the investigator for clinical evaluations at baseline (Day 1), Month 3, and Month 6/early termination (ET). Monthly assessments will follow a 28-day schedule, and at each visit and at any unscheduled visits, the subject's clinical status will be evaluated. All hospitalizations and all interventions (psychiatric only as well as pharmacy cost of all medications) will be recorded, in addition to all other assessments outlined in this protocol. The primary endpoint will be assessed at Month 3. The final trial visit will be on Month 6/ET and will be followed by a 30-day (± 3 day) safety follow-up period for subjects continuing on Abilify MyCite. For subjects completing Months 4 to 6 on standard of care, a 30-day safety follow-up period is not required. Subjects will also visit the clinic for medication dispensing and accountability at Months 1, 2, 4, and 5. Any treatment changes, including reason for the change, will be recorded in the electronic case report form (eCRF).

Evaluation of safety and tolerability of Abilify MyCite as assessed by frequency and severity of the adverse events (AEs) to be collected in this trial, ie, serious AEs (SAEs), device-related nonserious AEs, potential hepatotoxicity cases, and pregnancies.

Subject use of the Abilify MyCite system will be monitored by their respective investigators, who are suggested to review the physician dashboard data at a minimum of every 2 weeks and

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	<p>make changes to current treatment plan and therapy at their discretion. The investigators may request that a subject return to the site for unscheduled visits as deemed appropriate. In the event of an unscheduled visit, review of the investigator dashboard and safety events will be collected.</p> <p><u>Safety Follow-up</u></p> <p>All subjects who complete or withdraw from the trial while on Abilify MyCite (unless they have withdrawn their consent for participation in the trial) will receive a telephone call for safety follow-up at 30 days (\pm 3 days) after the last trial visit.</p> <p>This telephone contact will be made to assess if there were any AEs experienced since the last trial visit. In addition, the subject will be asked about any new medications or changes in existing medications and the information will be documented.</p>
<p>Subject Population:</p>	<p>The trial population will include male and female subjects, 18 to 65 years of age, inclusive, with a diagnosis of schizophrenia according to DSM-5 criteria. Subjects must have had at least 1 inpatient psychiatric hospitalization within 4 years (48 months) prior to screening. Subjects must have been prescribed oral antipsychotic treatment for at least 6 months or longer prior to screening. Approximately 493 subjects will be screened in order to enroll 320 subjects and complete 224 subjects.</p>
<p>Inclusion/Exclusion Criteria:</p>	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> • Subject must be willing and able to give written (signed and dated) informed consent, which includes adherence to trial requirements and restrictions before enrolling in the trial. Subject must be willing to adhere to trial procedures, including troubleshooting of the Abilify MyCite application (app) by a third party if needed. • Subject must be able to read and understand English. • Male and female subjects 18 to 65 years of age, inclusive, at the time of informed consent. • Subjects are deemed appropriate, per investigator judgment, to use Abilify MyCite and to enter this interventional trial. • Subject must possess a smartphone and is familiar with its use and is willing to download and interact with the Abilify MyCite app, completing all tasks as well as adequately operating all devices, as applicable. Caregiver/support person or other third party assistance can be utilized

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throughout participation in the trial. However, subjects should be encouraged to complete all tasks themselves. At the conclusion of the study, the caregiver/support person will be asked (where applicable) to provide feedback via the Caregiver Involvement Scale. A subject with a smartphone that is not compatible with the Abilify MyCite app will be offered a loaner phone for the trial period.

- Subject possesses the capacity to utilize the technology interfaces (eg, open and navigate software apps using the touch screen) and telephone features of a smartphone (Android or iOS). The subject has satisfactory mobile phone reception (preferably 3 bars or more or have wireless fidelity [Wi-Fi]) at home and/or at work for wireless carrier.
- Subject is cooperative, able to ingest oral medication, willing to complete all aspects of trial, and capable of reporting AEs.
- Clinical diagnosis of schizophrenia (defined by DSM-5) with a Positive and Negative Syndrome Scale (PANSS) total score between 60-90.
- Subjects currently prescribed oral atypical antipsychotic medication including aripiprazole or appropriate for aripiprazole treatment for 6 months or longer.
- Subjects are required to have had an inpatient hospitalization for schizophrenia within the last 48 months prior to entering the trial.
- Subject's general medical condition such that participation in the trial does not pose any additional risk as per investigator's judgment.
- Skin on the anterior chest just above the lower edge of the rib cage that is free of any dermatological problems (eg, dermatosis or dermatitis, open wounds, or other skin disorders such as warts, rashes, atopic dermatitis, or irritations).

Exclusion criteria

- Females who are breast-feeding and/or who are pregnant at the time of trial enrollment, or who plan to become pregnant during the trial.
- Sexually active males or women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the

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	<p>trial and for 30 days after the last dose of Abilify MyCite. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide.</p> <ul style="list-style-type: none"> • Any subject who participated in another clinical trial within 30 days of enrollment into the current trial. • Subjects who are currently being treated with an LAI antipsychotic or have been treated with an LAI in the retrospective 6-month phase. • Subjects with a current DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, bipolar I disorder, major depressive disorder (MDD), delirium, dementia, amnestic, or other cognitive disorders. Also, subjects with borderline, paranoid, histrionic, or antisocial personality disorder. • Subject with any disorder including but not limited to intellectual developmental delay or disorder, major neurocognitive disorder or other condition that may impact the subject’s ability to participate in the trial or interact with the smartphone application. • Subject who is likely to be incapable of using the Abilify MyCite technology, even with assistance. • Subject who has a history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere with assessments of safety or usability during the course of the trial, including but not limited to, hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the investigator. • Subject with a known allergy to adhesive tape or any pertinent components of the patch or aripiprazole tablet embedded with an IEM sensor (Abilify MyCite) product. • Any subject who, in the opinion of the investigator or the medical monitor, should not participate in the trial.
<p>Trial Site(s):</p>	<p>Approximately 75 sites</p>
<p>Device, Dose, Dosage regimen, Treatment period,</p>	<p>Abilify MyCite tracks drug ingestion and is composed of the following components:</p> <ul style="list-style-type: none"> • Aripiprazole tablet embedded with an IEM sensor (Abilify

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Formulation, Mode of Administration:	<p>MyCite).</p> <ul style="list-style-type: none"> • Abilify MyCite Patch (wearable sensor) that detects the signal from the IEM sensor after ingestion and transmits data to a smartphone. • Abilify MyCite App, a smartphone app, which is used with a compatible smartphone to display medication ingestion information for the subject. • Web-based portal or dashboard for investigators and caregivers.
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The treatment medication dose decision will be determined by the trial investigators independent from the protocol.

Initiation of Abilify MyCite treatment will commence at the baseline (Day 1) visit, with subjects ingesting the Abilify MyCite tablet embedded with an IEM sensor product, wearing the patch, and using the smartphone app for up to 6 months, including a required 3 months (Months 1 to 3) of Abilify MyCite treatment. This will be followed, at investigator discretion, to either change to standard-of-care antipsychotic treatment (eg, oral or LAI) or remain on Abilify MyCite for the second 3-month period (Months 4 to 6), during the prospective phase. The first dose of Abilify MyCite is to be taken at the baseline (Day 1) visit (in the clinic) during onboarding, unless they have already taken their daily dose. Subjects should not take their oral standard-of-care medication that morning before the baseline (Day 1) visit.

During the assessment period, subjects will visit the investigator for clinical evaluations at baseline (Day 1), Month 3, and Month 6/ET. Monthly assessments will follow a 28-day schedule. The primary endpoint will be assessed at Month 3. The final trial visit will be on Month 6/ET and will be followed by a 30-day (\pm 3 day) safety follow-up period for subjects continuing on Abilify MyCite. For subjects completing Months 4 to 6 on standard of care, a 30-day safety follow-up period is not required. Subjects will also visit the clinic for medication dispensing and accountability on Months 1, 2, 4, and 5. Any treatment changes, including reason for the change, will be recorded in the eCRF.

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<p>Trial Assessments:</p>	<p>Acceptance and Performance:</p> <ul style="list-style-type: none">• Using feedback from subjects, investigators, and caregivers/support person on the use of Abilify MyCite:<ul style="list-style-type: none">• [REDACTED]• [REDACTED]• [REDACTED]• [REDACTED] <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Safety: Safety will be assessed by SAEs, device-related nonserious AEs, potential hepatotoxicity cases, pregnancies, product quality complaints, and suicidality assessment.</p>
<p>Criteria for Evaluation:</p>	<p>Primary Endpoint:</p> <p>The primary endpoint is the comparison of inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization) between the retrospective period (Months 1 to 3) while subjects are on oral standard-of-care antipsychotic treatment and the prospective period (Months 1 to 3) after the subjects switch to Abilify MyCite.</p> <p>Secondary Endpoint:</p> <ul style="list-style-type: none">• Improved adherence based on overall PDC with Abilify MyCite versus retrospective oral atypical antipsychotics.

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Exploratory Endpoints:

- █ [REDACTED]
- █ [REDACTED]

[REDACTED]

- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]

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	<p style="text-align: center;">Safety Endpoints:</p> <p>Adverse events will be examined by frequency, severity, seriousness, and discontinuation (all cause and due to AEs). The safety and tolerability of Abilify MyCite, as assessed by the frequency and severity of SAEs, device-related nonserious AEs, potential hepatotoxicity cases, and pregnancies will be assessed along with an evaluation of any product quality complaints that arise. The Columbia Suicide Severity Rating Scale (C-SSRS) will be completed at baseline and all subsequent visits to assess the risk of suicide events and to classify reported suicide events.</p>
<p>Statistical Methods:</p>	<p>The primary endpoint of this trial is the comparison of inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization[s]) between the retrospective period (Months 1 to 3) while on oral standard-of-care antipsychotic treatment and the prospective period (Months 1 to 3) after the switch to Abilify MyCite. The analysis will be performed using a McNemar test on those who have hospitalization data during Months 1 to 3 prior to the screening period and during Months 1 to 3 after switch to Abilify MyCite.</p> <p>The sample size calculation assumes that 15.5% of subjects are hospitalized during retrospective Month 1 to 3 and 7% are hospitalized during prospective Month 1 to 3; about 5% of subjects who are not hospitalized retrospective will be hospitalized prospective while 13.5% of subjects who are hospitalized retrospective will not be hospitalized.</p> <p>Two interim analyses are planned when 50% and 70% of subjects have completed the prospective phase (3 months).</p> <p>With the above assumption and 2 interim analysis, 224 completed subjects will provide 80% power and conserve the overall Type I error at 0.05 level in order to detect a</p>

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	<p>difference of 8.5% in 2 paired hospitalization proportions between retrospective and prospective periods while the proportion of total discordant pairs is 18.5%. This sample size is based on the 3 sequential tests that are made using LanDeMets Spending Function with O'Brien-Fleming boundary; a futility conditional power of 15% is built in the sample size calculation to allow the trial to stop for futility. Based on the conditional power and the alpha level at the interim analysis, the trial could stop for efficacy or futility, continue with the initial planned 224 sample size or increase to up to 300 sample size if the conditional power falls between 30% and 80% at interim.</p> <p>The 2-sided alpha levels for these 2 interim analyses are 0.00312 and 0.0139 respectively, and the alpha left for the final analysis will be 0.04528.</p> <p>In general, baseline measurements of safety variables are defined as the last measurements prior to the first dosing of Abilify MyCite for the prospective phase of the trial. All safety summaries will be descriptive in nature.</p>
Trial Duration:	<p>The duration of this trial from first subject enrolled to first subject completed is estimated to be up to approximately 8.5 months including a 45-day screening period and a 6 month prospective phase that includes a required 3 months (Months 1 to 3) of Abilify MyCite treatment. This will be followed, at investigator discretion, to either change to standard-of-care antipsychotic treatment (eg, oral or LAI) or remain on Abilify MyCite for the second 3-month period (Months 4 to 6), during the prospective phase. The final trial visit will be on Month 6/ET and will be followed by a 30-day (\pm 3 day) safety follow up period for subjects continuing on Abilify MyCite. For subjects completing Months 4 to 6 on standard of care, a 30-day safety follow-up period is not required. Subjects will also visit the clinic for medication dispensing and accountability on Months 1, 2, 4, and 5. Any treatment changes, including reason for the change, will be recorded in</p>

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the eCRF. Total length of participation in the trial will vary depending on the screening duration and if the subjects remain on Abilify MyCite treatment.

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List of Abbreviations and Definitions of Terms

<u>Abbreviation</u>	<u>Definition</u>
AE	Adverse event
app	Application
CGI-I	Clinical Global Impression - Improvement of Illness Scale
CGI-S	Clinical Global Impression - Severity of Illness Scale
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
eICF	Electronic informed consent form
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEM	Ingestible event marker
IND	Investigational new drug
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-Treat
LAI	Long-acting injectable
MDD	Major depressive disorder
N or n	Number of subjects
PANSS	Positive and Negative Syndrome Scale
PDC	Proportion of days covered
PQC	Product Quality Complaint
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
Wi-Fi	Wireless fidelity
WOCBP	Women of childbearing potential

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Definition of Terms

Level of Care	Description
Assertive Community Treatment	Team treatment approach designed to provide comprehensive, community-based psychiatric treatment, rehabilitation, and support to persons with serious and persistent mental illness such as schizophrenia. Provides highly individualized services directly to consumers. Recipients receive the multidisciplinary, round-the-clock staffing of a psychiatric unit, but within the comfort of their own home and community. To have the competencies and skills to meet a client's multiple treatment, rehabilitation, and support needs, team members are trained in the areas of psychiatry, social work, nursing, substance abuse, and vocational rehabilitation. The assertive community treatment team provides these necessary services 24 hours per day, 7 days per week, and 365 days per year.
Emergency Room Visit	Medical treatment facility, specializing in acute care of subjects who present without prior appointment, either by their own means or by ambulance. Due to the unplanned nature of subject attendance, the department must provide initial treatment for a broad spectrum of illnesses and injuries, some of which may be life-threatening and require immediate attention. The medical condition may require inpatient admission or release back to the community for ongoing outpatient treatment.

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1 Introduction

Abilify MyCite[®] (aripiprazole tablets with sensor) is a drug-device combination product comprised of aripiprazole tablets embedded with an ingestible event marker (IEM) sensor intended to track drug ingestion that is indicated for¹:

- Treatment of adults with schizophrenia.
- Treatment of bipolar I disorder:
 - Acute treatment of adults with manic and mixed episodes as monotherapy and as adjunct to lithium or valproate.
 - Maintenance treatment of adults as monotherapy and as adjunct to lithium or valproate.
- Adjunctive treatment of adults with major depressive disorder (MDD).

Abilify MyCite tracks drug ingestion and is composed of the following components¹:

- Aripiprazole tablet embedded with an IEM sensor (Abilify MyCite).
- Abilify MyCite Patch (wearable sensor) that detects the signal from the IEM sensor after ingestion and transmits data to a smartphone.
- Abilify MyCite App, a smartphone application (app), which is used with a compatible smartphone to display medication ingestion information for the subject.
- Web-based portal or dashboard for investigators and caregivers.

This trial will utilize the clinical supply of Abilify MyCite.

The Abilify MyCite system has been tested in subjects with serious mental illness, with clinical trials demonstrating an ability to report tablet ingestion with high accuracy and acceptable latency time, with positive results regarding usability reported by both subjects and investigators/caregivers.^{2,3,4,5,6,7,8,9,10}

Food and Drug Administration (FDA) approval of Abilify MyCite was also based, in part, on evidence from human factors engineering studies, which were conducted to ensure safe and effective use of the system.¹¹ Future studies to assess ability to monitor and improve adherence and other clinical outcomes will be important.

The Abilify MyCite system is a drug-device combination product comprised of aripiprazole (an atypical antipsychotic) tablets embedded with a sensor that communicates with a patch (wearable sensor) and a medical software application with collected information (ingestion, mood, activity, rest) tracked and summarized for

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subjects, investigators, and potentially caregivers. Abilify MyCite is intended to track drug ingestion and is indicated for the treatment of adults with schizophrenia, bipolar I disorder (acute treatment of adults with manic and mixed episodes or maintenance treatment of adults), and adjunctive treatment of adults with MDD.¹ Abilify MyCite can provide objective subject data with regard to medication-taking behaviors and activities that can enable clinicians to make more informed and optimal therapeutic decisions. Additionally, the Abilify MyCite system allows subjects to engage in taking a more active role in their personal wellbeing. The Abilify MyCite system fulfills an unmet need regarding medication adherence monitoring in these subjects.

Currently available methods for monitoring adherence have limitations; as such, an unmet need exists for a simple, accurate solution for adherence monitoring to enable investigators to objectively measure whether a subject was adherent to treatment. Increasing investigator awareness of subject nonadherence and its role in suboptimal response may allow for better treatment decision making and allow an opportunity for more investigator/subject engagement in care. The available evidence suggests that subject engagement or activation in serious mental illness, while not a main focus in clinical practice, may provide substantial benefit to subject health outcomes, including management of comorbid conditions, and should be encouraged.

The Abilify MyCite system may be used by investigators who desire accurate, timely, and objective measures of medication adherence over a defined period of time to aid in their treatment decisions. It also allows investigators to make treatment decisions based on objective medication ingestion data, rather than guessing whether suboptimal response is based on poor adherence or limited effectiveness. For subjects, Abilify MyCite offers access to objective personal data on medication-taking behaviors and other measures such as self-reported mood over time and activity and rest patterns. This healthcare information is then available to both the subject and investigator (and caregivers with subject consent), which may aid in increased health awareness and more informed shared decision making regarding treatment.

Although a large number of pharmacological treatments exist, the management of serious mental illness presents a significant personal and societal burden. For treatments to be effective, the subject must be adherent to their medication. Although many methods are used to measure adherence, studies have shown widespread nonadherence in psychiatric populations. Cramer and Rosenheck found average adherence rates of 58% and 65% for antipsychotics and antidepressants, respectively, compared with an adherence rate of 76% for nonpsychiatric medications.¹² This finding is problematic due to the relationship

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between nonadherence and disease burden. Consequently, nonadherence to psychiatric medications remains a major barrier to achieving optimal health outcomes in this population and ensuring medication compliance is an unmet medical need.^{12,13}

The components of Abilify MyCite are shown in Figure 1-1 and an overview of the Abilify MyCite system is shown in Table 1-1.



Figure 1-1 Abilify MyCite Components

Table 1-1 Overview of Abilify MyCite System	
Characteristic	Description
Components	<ul style="list-style-type: none"> • Aripiprazole tablet embedded with an IEM sensor (Abilify MyCite). • Abilify MyCite Patch (wearable sensor) that detects the signal from the IEM sensor after ingestion and transmits data to a smartphone. • Abilify MyCite App (a smartphone app which is used with a compatible smartphone to display information for the subject). • Web-based portal for investigators and caregivers.
FDA-approved indication	<ul style="list-style-type: none"> • A drug-device combination product comprised of aripiprazole tablets embedded with an IEM sensor intended to track drug ingestion that is indicated for the treatment of adults with schizophrenia; treatment of bipolar I disorder (including acute treatment of adults with manic and mixed episodes as monotherapy and as adjunct to lithium or valproate, or as maintenance treatment of adults as monotherapy and as adjunct to lithium or valproate); and adjunctive treatment of adults with MDD.

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Table 1-1 Overview of Abilify MyCite System	
Characteristic	Description
Limitations of use	<ul style="list-style-type: none"> The ability of Abilify MyCite to improve subject compliance or modify aripiprazole dosage has not been established. The use of Abilify MyCite to track drug ingestion in “real-time” or during an emergency is not recommended because detection may be delayed or not occur.

The Abilify MyCite system includes an ingestible sensor to confirm ingestion of Abilify MyCite when the sensor is activated in the stomach. The sensor activation signal and the information about medication ingestion and other physiological metrics are gathered by a compatible wearable sensor that relays that information to a mobile app for the subject and to web-based software that can display information for an investigator or caregiver. The Abilify MyCite system is composed of the following components (Figure 1-1 and Table 1-1)^{1,2}:

- Aripiprazole tablet embedded with an IEM sensor (Abilify MyCite). The IEM is a 1 mm sized ingestible device embedded in the Abilify MyCite tablet. Upon contact with gastric fluid, magnesium and cuprous chloride within the IEM react to activate and power the device. The IEM then communicates to the Abilify MyCite Patch (wearable sensor) to track aripiprazole ingestion.
- Abilify MyCite Patch (wearable sensor) that is designed to detect the ingestion of the Abilify MyCite tablet, record the ingestion of the IEM, and transmit ingestion data to the mobile subject application. These data include the date and time of ingestion and the unique identification number of the ingestible device. The patch also records physiological metrics (activity level via step count and body position) and transmits these data to a compatible mobile device.
- Abilify MyCite App (a smartphone app which is used with a compatible smartphone to display information for the subject) to allow subjects to review their medication ingestion as well as enter their behavioral data (subject rated mood and quality of rest). These data can be shared with investigators and caregivers with the subject’s consent.
- Web-based portal for investigators and caregivers provides an interface to review data shared by a subject.

1.1 Nonclinical Data

Please refer to the Investigator’s Brochure (IB) for more detailed information regarding nonclinical data.¹⁴

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1.2 Clinical Data

Please refer to the IB for more detailed information.¹⁴

1.3 Known and Potential Risks and Benefits

1.3.1 Risks Related to the Abilify MyCite System

1.3.1.1 Skin Findings at the Site of the Patch Attachment

The most common adverse events (AEs) associated with the patch in previous trials have been related to skin irritation at the site of the patch placement. This phenomenon has generally been mild in intensity, involving itching, localized redness, small papules, and/or elevation of the skin under or at the edges of the adhesive. Fine scabbing at the edges of the patch occurred rarely without significant ulceration. The mechanism of these skin changes, which are transient in nature, is related to irritant contact dermatitis, a nonimmune-mediated phenomenon that is commonly seen with adhesive medical products, arising from mechanical irritation, chemical irritation, and decreased breathability of the skin under the patch. In a small number of cases, irritant contact dermatitis leads to transient discoloration of the skin that may last weeks to months.

Several mitigations will be implemented to reduce the risk of these hazards. From a materials standpoint, the patch has been designed and manufactured under Good Manufacturing Practices from components and medical-grade materials that have individually passed required biocompatibility testing. These facts underpin a favorable biocompatibility assessment of the patch.

Skin will be monitored for irritation or changes at the site(s) of patch placement by the investigators during investigator visits. Subjects will be trained to self-monitor their skin at the sites of patch placement between investigator visits. The patches will be replaced during the trial. Should skin changes arise, then the simplest intervention will be to move the patch to a different site on the torso. Subjects will also be told that they are free to remove the patch at any time, and that if they do they must inform trial staff immediately. Subjects whose frequency or intensity of skin changes is unacceptable can be withdrawn from the trial by the investigators.

Finally, since the patch has an adhesive backing for long-term wear, some skin irritation may result from removing the patch because it retains a significant amount of adhesion. To reduce this possibility, subjects may be provided adhesive remover wipes, which can be used to ease any discomfort from patch removal. If the patch falls off, the subject

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should replace it with another available patch and inform the site staff. Abilify MyCite is not expected to add any appreciable risk to the inherent risks of the trial population.

1.3.1.2 Allergic Reaction

An allergic reaction could potentially arise from exposure to components of Abilify MyCite product or the patch, including the following: Adhesive on the patch; microchip of the IEM; minerals of the IEM; excipient materials in the IEM and IEM tablet dose forms; excipient materials in the IEM formulations; and/or dyes used in the IEM formulations.

To mitigate the risk of this potential hazard, prospective subjects who have a known allergy to any of the components listed above will be excluded from the trial. Allergy to tape will be specifically queried. Trial subjects will be monitored for symptoms and signs of allergic reaction throughout the course of the trial. If symptoms should arise, the subject will be treated promptly and accordingly.

1.3.1.3 Changes in Stool Habits

The majority of the excipient materials used in the Abilify MyCite product (and internal components of the IEM formulations) are cellulose-based. Cellulose in high oral doses is commonly used as a stool softener. Stool softeners typically increase the bulk and potentially the frequency of bowel movements, but they rarely cause diarrhea. However, the quantities of cellulose-based excipients in a daily dose of Abilify MyCite product in this trial are several fold smaller than the therapeutic dose used for stool-softening purposes.

Therefore, it is the opinion of the sponsor that the probability of changes in stool habits is low and, were they to occur, the clinical implications would likely be minor.

1.3.1.4 Anxiety from the Use of the Abilify MyCite System

Subjects may experience anxiety related to swallowing the Abilify MyCite product, wearing the patch, or using the smartphone. Moreover, it is theoretically possible that subjects could feel uncomfortable with the concept of 24-hour data collection. To reduce potential subject anxiety, adequate training time along with clinical and technical support will be made readily available during the trial. Moreover, familiarity with a smartphone is an inclusion criterion (see [Section 3.4.2](#)).

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1.3.1.5 Potential Theoretical Abilify MyCite System-related Risks

1.3.1.5.1 Procedure-Related Risks

1.3.1.5.1.1 Communications-related Risks

Subjects will be required to use a mobile smartphone during the trial to upload and later to view data. Through misapprehension of the use instructions or technical failures, subjects could experience confusion or frustration.

To mitigate this problem, only the subjects who have the capacity to utilize the technology interfaces (eg, open and navigate software applications using the touch screen) and telephone features of a smartphone will be enrolled in this trial.

Moreover, subject privacy is essential. It is theoretically possible that in the process of communicating through the app, privacy could become compromised. This could occur when data are being transmitted by the app.

To mitigate this risk, industry-standard encryption protocols will be used for data transmission from the patch to the computing device and from the computing device to the server via the cellular network. The access information for the app data are stored only on the sponsor's servers, which are also protected with industry-standard security features.

All aspects of the app are compliant to Health Insurance Portability and Accountability Act of 1996 requirements and European General Data Protection Regulation.

Therefore, it is the opinion of the sponsor that the risk of adverse clinical consequences from the planned trial communications is very low.

1.3.1.5.1.2 Less Significant Procedure-related Risks

Subjects may feel uncomfortable about answering personal health questions. The risks are very unlikely to result in significant adverse clinical outcomes, but research personnel will be sensitive to this issue.

1.3.2 Benefits Related to the Abilify MyCite System

There is a potential benefit from participating in the trial, in that subjects may have a better understanding of their medication-taking pattern and the relationship to their illness. In addition, subjects may have a better understanding of their personal physiologic status (eg, activity, rest) by viewing the individualized health data on their smartphone.

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The sponsor's intent is to develop a system that will be of significant benefit to future subjects by providing a novel, convenient method to track medication-taking behavior in an objective manner, and to monitor important physiologic parameters on an ambulatory basis. The execution of the present trial would represent an opportunity to gather feedback regarding the use of the app in the trial population. Thus, data gathered in the trial will be important for refining the app to help future subjects who may use the system.

1.3.2.1 Potential Benefits Related to the Abilify MyCite System

The Abilify MyCite product includes an app providing an advance on the available proxy measured by the following:

- Ability to provide confirmation of medication ingestion thereby enabling accurate detection of subject adherence status.
- Ability to provide information to assess whether uncontrolled symptoms may be explained by nonadherence or indicate treatment nonresponse.
- Ability to assess adherence on a continuous (near real-time) basis.
- Ability to provide adherence electronic feedback to subject, investigator, and/or caregiver/support person (if applicable).

The sponsor's intent is to develop a system that will benefit future subjects by providing the ability to track their medication-taking behavior in an objective manner and being able to monitor several physiologic parameters.

2 Trial Rationale and Objectives

2.1 Trial Rationale

Poor adherence to medication is a major barrier to the treatment of psychiatric disorders. Mobile health and digital medicine technologies have become available to subjects and consumers that may improve health management and medication compliance.¹⁵

Therefore, Otsuka Pharmaceutical Co., Ltd (Otsuka) has developed Abilify MyCite to track drug ingestion. Each aripiprazole tablet is embedded with an IEM. When swallowed, and after reaching the stomach, the IEM transmits a signal that is detected and recorded by a patch worn on the subject's torso. The patch transmits data to the subject's mobile device (ie, smartphone), which uploads data to a secure, cloud-based server. Use of Abilify MyCite will allow subjects to view their aripiprazole ingestion data on their mobile device; in this way, the subject can learn about their medication ingestion

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patterns, which could enable greater subject awareness and self-management of their disease.

In addition, the subject's investigators and elected caregivers can view data via a web-based portal served by the cloud-based server.¹ With Abilify MyCite tracking drug ingestion, psychiatric hospitalizations should be reduced when compared to standard-of-care antipsychotic treatment; this reduction is anticipated to be driven by an improvement in timely and appropriate treatment decisions based on objective data. Therefore, use of Abilify MyCite is expected to reduce overall healthcare utilization.

2.2 Dosing Rationale

The subjects in this trial will receive Abilify MyCite as dispensed by their investigator. The treatment medication decision will be determined by the investigators and independent from the protocol.

2.3 Trial Objectives

2.3.1 Primary

To compare inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalizations) between the retrospective period (Months 1 to 3) while subjects are on oral standard-of-care antipsychotic treatment and the prospective period (Months 1 to 3) after the subjects switch to Abilify MyCite.

2.3.2 Secondary

To evaluate improved adherence of Abilify MyCite based on overall proportion of days covered (PDC).

To further evaluate long-term safety and tolerability of Abilify MyCite.

3 Trial Design

3.1 Type/Design of Trial

This is a phase 3b, open-label, prospective, clinical trial designed to assess the difference between inpatient psychiatric hospitalization rates in subjects on oral standard-of-care antipsychotic treatment(s) for a period of 6 months followed by a switch to Abilify MyCite for a period of 3 months (Months 1 to 3). At the Month 3 visit, the investigator should decide if subjects will continue on Abilify MyCite for an additional 3 months (Months 4 to 6) or switch to a standard-of-care treatment (eg, oral atypical antipsychotics or a long acting injectable [LAI]) for the duration of treatment.

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This trial will include male and female subjects who are 18 to 65 years of age, inclusive, with a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Subjects must have had at least 1 inpatient psychiatric hospitalization within 4 years (48 months) and must have been prescribed oral antipsychotics for at least 6 months or longer prior to screening.

Subjects will enter a screening period (up to 45 days). If deemed eligible to participate, subjects will enter an open-label Abilify MyCite treatment prospective phase for up to 6 months.

Oral Standard-of-Care Antipsychotic Treatment(s) (Retrospective Phase)

To be eligible for trial participation, subjects must have been prescribed oral antipsychotic standard-of-care pharmacotherapy for at least 6 months or longer, with evidence of prescription (ie, pharmacy records) during the retrospective phase and prior to screening. Subjects administered antipsychotics other than aripiprazole must cross-titrate onto oral aripiprazole during the screening period at the discretion of the investigator to be eligible for trial participation.

Screening

After providing informed consent, subjects will enter the 45-day (Days -45 to -1; approximately 6 weeks) screening period to determine if they are eligible to enter the Abilify MyCite treatment (prospective) phase. The subject's past psychiatric history for the 6 months prior to screening must be available, inclusive of a comprehensive review of all psychiatric hospitalizations and interventions (psychiatric only).

As safety of the subject dictates, 2 options are available to the investigator as subjects transition from the screening period to the Abilify MyCite treatment (prospective) phase:

- 1) Antipsychotic medications other than oral aripiprazole may be tapered off and/or discontinued during the screening period prior to the subject receiving the first treatment with Abilify MyCite.
- 2) Antipsychotic medications other than oral aripiprazole may be continued during the screening period and cross-titration with oral aripiprazole trial drug may occur. Some investigators may choose this option for the subject depending as local practice patterns dictate and on the subject's safety (see [Section 3.2.1](#)).

Abilify MyCite treatment (prospective) phase

For subjects enrolled in the trial, those not on aripiprazole at screening and who need to cross-titrate will do so during the screening period for conversion to aripiprazole from

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other antipsychotics according to the approved labels. At the baseline visit (Day 1), Abilify MyCite onboarding (see [Section 3.2.2.2](#)) will be provided with informational materials and additional call center support. Initiation of Abilify MyCite treatment will commence at the baseline (Day 1) visit, with subjects ingesting the Abilify MyCite tablet embedded with an IEM sensor product, wearing the patch, and using the smartphone app for up to 6 months, including a required 3 months (Months 1 to 3) of Abilify MyCite treatment. This will be followed, at investigator discretion, to either change to oral standard-of-care antipsychotic treatment (eg, oral or LAI) or remain on Abilify MyCite for the second 3-month period (Months 4 to 6), during the prospective phase. The first dose of Abilify MyCite is to be taken at the baseline (Day 1) visit (in the clinic) during onboarding, unless they have already taken their daily dose. Subjects should not take their oral standard-of-care medication that morning before the baseline (Day 1) visit.

During the assessment period, subjects will visit the investigator for clinical evaluations at baseline (Day 1), Month 3, and Month 6/early termination (ET). Monthly assessments will follow a 28-day schedule, and at each visit and at any unscheduled visits, the subject's clinical status will be evaluated. All hospitalizations and all interventions (psychiatric only as well as pharmacy cost of all medications) will be recorded, in addition to all other assessments outlined in this protocol. The primary endpoint will be assessed at Month 3. The final trial visit will be on Month 6/ET and will be followed by a 30-day (\pm 3 day) safety follow-up period for subjects continuing on Abilify MyCite. For subjects completing Months 4 to 6 on standard of care, a 30-day safety follow-up period is not required. Subjects will also visit the clinic for medication dispensing and accountability at Months 1, 2, 4, and 5. Any treatment changes, including reason for the change, will be recorded in the electronic case report form (eCRF).

Evaluation of safety and tolerability of Abilify MyCite as assessed by frequency and severity of the AEs to be collected in this trial, ie, serious AEs (SAEs), device-related nonserious AEs, potential hepatotoxicity cases, and pregnancies.

Subject use of the Abilify MyCite system can be monitored by their respective investigators, who are suggested to review the physician dashboard data at a minimum of every 2 weeks and make changes to current treatment plan and therapy at their discretion. The investigators may request that a subject return to the site for unscheduled visits as deemed appropriate. In the event of an unscheduled visit, review of the investigator dashboard and safety events will be collected.

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Safety Follow-up

All subjects who complete or withdraw from the trial while on Abilify MyCite (unless they have withdrawn their consent for participation in the trial) will receive a telephone call for safety follow-up at 30 days (\pm 3 days) after the last trial visit.

This telephone contact will be made to assess if there were any AEs experienced since the last trial visit. In addition, the subject will be asked about any new medications or changes in existing medications and the information will be documented. The trial design is presented in [Figure 3.1-1](#).

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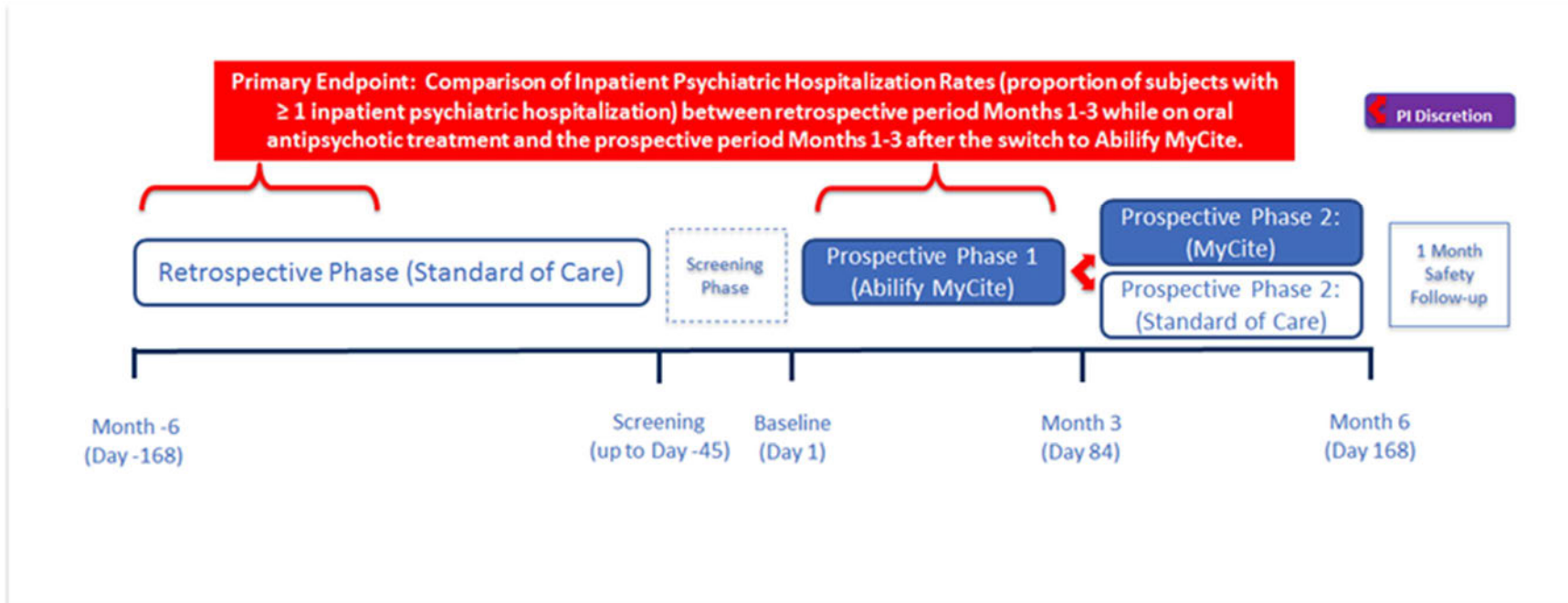


Figure 3.1-1 Trial Design Schematic

Note: Monthly assessments will follow a 28-day schedule.

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3.2 Trial Treatments

3.2.1 Tolerability Assessment/Cross-Titration

Subjects who have no history of tolerating oral aripiprazole will be assessed for tolerability to oral aripiprazole or be cross-titrated to oral aripiprazole at the discretion of the investigator. The recommended procedure for initiation of oral aripiprazole is an ascending cross-titration scheme according to consensus guidelines from a multidisciplinary panel^{16,17} and the procedure as it pertains to this protocol is summarized in [Table 3.2.1-1](#).

	First Week^a	Second Week^b	Third Week	Fourth Week	Fifth Week	Sixth Week
Non-generic aripiprazole dose (trial drug)	Initially 5 mg, increasing to 10 mg	10 mg	10 or 15 mg	10 or 15 mg	10 or 15 mg	10 or 15 mg ^c
Dose of other antipsychotic(s)	No change	No change	Decrease	Decrease or D/C ^d	Decrease or D/C ^d	D/C ^d

D/C = discontinue

^aAdd short-term concomitant medications as needed to control symptoms (eg, agitation, insomnia, and nausea).

^bGradually withdraw concomitant medications.

^cMonotherapy with oral aripiprazole will begin no later than Week 6. The target starting dose for monotherapy may be > 15 mg, depending on investigator judgment and the subject's clinical need.

^dThe other antipsychotic treatment(s) can be discontinued at Week 4 or any time thereafter up to, and including, Week 6. The subject will enter the oral stabilization phase the day after discontinuation of all other antipsychotic treatment(s), or after a minimum of one cycle plus 14 days has elapsed if the subject received an approved long-acting antipsychotic treatment prior to enrollment (eg, 2-week cycle plus an additional 14 days for risperidone long-acting injection) or 60 days have elapsed for investigational long-acting antipsychotics.

The following subjects may proceed directly to the Abilify MyCite treatment (prospective) phase without prior cross-titration to oral aripiprazole at the discretion of the investigator:

- Subjects receiving oral aripiprazole monotherapy at screening, or
- Subjects currently taking any antipsychotic other than oral aripiprazole at screening and have a history of tolerating oral aripiprazole.

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The purpose of the tolerability assessment/cross-titration is to evaluate for potential allergy to aripiprazole and the subject's clinical status prior to Abilify MyCite treatment. Subjects will be seen in the clinic for up to 45 days, until tolerability to oral aripiprazole has been determined, based on investigator discretion, or until the subject is terminated from the trial.

The recommended initial dose of oral aripiprazole is 10 mg or 15 mg/day, depending on the subject's symptoms and the investigator's judgment. The investigator may titrate the dose of oral aripiprazole up to 30 mg/day as deemed appropriate. Some investigators may choose this option for the subject depending as local practice patterns dictate and on the subject's safety.

Subjects may proceed to the Abilify MyCite treatment (prospective) phase after 1 week if they tolerate oral aripiprazole according to the investigator's judgment.^{16,17} If a subject cannot tolerate oral aripiprazole, or requires inpatient psychiatric hospitalization based on the investigator's clinical judgment, the subject will be withdrawn from the trial.

Subjects who routinely take their oral aripiprazole in the morning are not to take the oral dose on the morning of clinic visits, so that adjustments to the dose can be made, as required. Oral aripiprazole will be administered at the clinic after all assessments have been completed.

3.2.2 Abilify MyCite Treatments

The subjects will receive Abilify MyCite as prescribed by their investigators. The subject and the investigator will initiate the system at the baseline (Day 1) visit and use it for up to 6 months, including a required 3 months (Months 1 to 3) of Abilify MyCite treatment. This will be followed, at investigator discretion, to either change to standard-of-care antipsychotic treatment (eg, oral or LAI) or remain on Abilify MyCite for the second 3-month period (Months 4 to 6) during the prospective phase. The first dose of Abilify MyCite is to be taken at the baseline (Day 1) visit (in the clinic) during onboarding (Section 3.2.2.2), unless they have already taken their daily dose. Subjects should not take their oral standard-of-care medication that morning before the baseline (Day 1) visit. Following this period, the use of Abilify MyCite will be stopped and the subject will return to standard-of-care (routine follow-up from care teams and continue standard-of-care medications). Subjects will have access to their trial account or data in the smartphone app until 1 month after the last subject's Month 6/ET visit. After this duration, the subjects will no longer have access to their data.

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Subjects will also visit the clinic for medication dispensing and accountability during the prospective phase at Months 1, 2, 4, and 5. Any treatment changes, including reason for the change, will be recorded in the eCRF.

3.2.2.1 Abilify MyCite Components and Use

Abilify MyCite includes a drug-device combination of an aripiprazole tablet embedded with an IEM sensor product, a patch, and an application software to convey level of activity and rest, and to mark events through the act of ingestion.

The patch is a separate compatible medical device, which consists of a wearable sensor and an associated compatible medical device software application. The patch is an unmedicated adhesive device that is worn within a specified torso area on the left side. The patch detects and time-stamps each IEM ingestion as well as measures and records other date- and time-stamped physiologic and behavioral data, such as heart rate, physical activity (ie, step count), and amount of rest. The patch connects wirelessly to a commercially available mobile computing device (ie, smartphone) to transfer data captured by the patch via the compatible medical device software application to a secure server for aggregation and processing.

The software application, which include elements that reside both locally (eg, on a mobile computing device) and remotely (eg, on remote server), enable data transfer and display on the subject's mobile computing device (ie, smartphone) and on the physician web-based dashboard. As part of the software application, subjects may enter their subjective rest quality on a daily basis and their subjective mood rating up to several times a day.

Subjects should own a commercially available smartphone and be familiar with its use. A subject with a smartphone that is not compatible with the Abilify MyCite app will be offered a loaner phone for the trial period. The smartphone should be charged daily (however, it is noted that if the smartphone battery becomes fully depleted, the application data will not be lost, as the data will remain stored on the patch). Subjects will be requested to carry the smartphone with them as much as possible, and to plug in the device at a dedicated location at home where they have easy and frequent access when not being carried. The preferred location is on a bedside table or location immediately adjacent to where the subject sleeps.

The subject may view his/her data at will on the smartphone. In addition, the subject's selected investigators and selected caregivers/support person (if applicable) can view this

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information via the cloud-based server. Investigators can set up missed dose notifications to monitor any lapses in subject's adherence.

Each investigator will be provided with a printed Abilify MyCite application reference guide that will provide explicit directions for normal use and troubleshooting. At each visit, subjects will be reminded by the investigator to contact the call center with any technical questions about the application. If there are any technical issues with the application that the call center is unable to resolve, the subject will be routed to a technology support representative. If a subject contacts the call center with clinical issues including reporting of SAEs, the call center will document the event and forward the information to the trial site for additional follow-up, as needed.

3.2.2.2 Abilify MyCite System Onboarding

Onboarding involves the pairing of a patch with the application contained on a smartphone and then applying that patch to the skin in the proper location.

During the Abilify MyCite onboarding process, the smartphone app will provide guidance for skin preparation and patch placement. A simple skin preparation procedure, consisting of gently cleaning the skin surface and allowing the area to dry, is recommended. On some subjects, clipping of body hair in the placement zone may be required to allow secure device adhesion. Placement of the patch should avoid locations below the bottom of the rib cage or areas where the patch was previously worn. Use of lotions on the skin where the patch will be placed is not recommended. The patch can be worn during regular activities including showering, but new patches should not be applied for a few hours after showering or other physical activities to ensure the adhesive sticks properly. The smartphone app will remind subjects when the patch needs to be changed.

3.2.2.3 Abilify MyCite System Patch Use

Throughout the assessment period, the subject will be notified by the smartphone app when the patch needs to be changed. No patch should remain applied to a subject's skin for longer than the intended patch duration.

Following the initial patch pairing and placement during the baseline visit, a subject will be instructed to wear a patch continuously (eg, 24 hours per day, 7 days per week), if possible. The patch can be worn throughout different daily activities, including bathing and swimming.

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A subject will be told that it is allowable to remove the patch for any reason (especially for evidence of local skin irritation/inflammation), but that it is preferred that the patch be kept on as much as is tolerable and safe. The subject should note, as much as possible, the events surrounding any premature removal of the patch and contact the site immediately. A reason must be recorded for every patch removal, including reasons for premature patch removal, in the eCRF. Subjects are free to replace a patch offsite using dispensed trial supplies.

Each subject will return all supplies, including all used patches and associated labels, to the trial site. At the end of the trial (Month 6/ET visit), all returned patches and associated labels will be destroyed at the trial site(s) or by a designated agent.

3.3 Trial Population

The trial population will include male and female subjects, 18 to 65 years of age, inclusive, with a diagnosis of schizophrenia according to DSM-5 criteria. Subjects must have had at least 1 inpatient psychiatric hospitalization within 4 years (48 months) prior to screening. Subjects must have been prescribed oral antipsychotic treatment for at least 6 months or longer prior to screening. Approximately 493 subjects will be screened in order to enroll 320 subjects and complete 224 subjects.

3.3.1 Number of Subjects and Description of Population

3.3.2 Subject Selection and Numbering

All subjects will be given a unique 5-digit subject identification number after signing the informed consent form (ICF).

3.4 Eligibility Criteria

3.4.1 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 Institutional Review Board (IRB) that approves this protocol. Additionally, the informed consent will cover the retrospective, screening, and prospective aspects of the trial.

Each ICF will comply with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site-specific ICF used in the trial before submission to the IRB.

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The 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 prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s).

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

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

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

Eligible participants include adult subjects with a current diagnosis of schizophrenia being treated with aripiprazole, or for whom aripiprazole treatment would be appropriate, as determined by the treating physician. Subjects must also meet all of the inclusion criteria ([Section 3.4.2](#)) and none of the exclusion criteria ([Section 3.4.3](#)).

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in [Table 3.4.2-1](#).

1.	Subject must be willing and able to give written (signed and dated) informed consent, which includes adherence to trial requirements and restrictions before enrolling in the trial. Subject must be willing to adhere to trial procedures, including troubleshooting of the Abilify MyCite app by a third party if needed.
2.	Subject must be able to read and understand English.
3.	Male and female subjects 18 to 65 years of age, inclusive, at the time of informed consent.
4.	Subjects are deemed appropriate, per investigator judgment, to use Abilify MyCite and to enter this interventional trial.

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Table 3.4.2-1 Inclusion Criteria	
5.	Subject must possess a smartphone and is familiar with its use and is willing to download and interact with the Abilify MyCite app, completing all tasks as well as adequately operating all devices, as applicable. Caregiver/support person or other third party assistance can be utilized throughout participation in the trial. However, subjects should be encouraged to complete all tasks themselves. At the conclusion of the study, the caregiver/support person will be asked (where applicable) to provide feedback via the Caregiver Involvement Scale. A subject with a smartphone that is not compatible with the Abilify MyCite app will be offered a loaner phone for the trial period.
6.	Subject possesses the capacity to utilize the technology interfaces (eg, open and navigate software applications using the touch screen) and telephone features of a smartphone (Android or iOS). The subject has satisfactory mobile phone reception (preferably 3 bars or more or have Wi-Fi) at home and/or at work for wireless carrier.
7.	Subject is cooperative, able to ingest oral medication, willing to complete all aspects of trial, and capable of reporting AEs.
8.	Clinical diagnosis of schizophrenia (defined by DSM-5) with a PANSS total score between 60-90.
9.	Subjects currently prescribed oral atypical antipsychotic medication including aripiprazole or appropriate for aripiprazole treatment for 6 months or longer.
10.	Subjects are required to have had an inpatient hospitalization for schizophrenia within the last 48 months prior to entering the trial.
11.	Subject's general medical condition such that participation in the trial does not pose any additional risk as per investigator's judgment.
12.	Skin on the anterior chest just above the lower edge of the rib cage that is free of any dermatological problems (eg, dermatosis or dermatitis, open wounds, or other skin disorders such as warts, rashes, atopic dermatitis, or irritations).

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in [Table 3.4.3-1](#).

Table 3.4.3-1 Exclusion Criteria	
1.	Females who are breast-feeding and/or who are pregnant at the time of trial enrollment, or who plan to become pregnant during the trial.
2.	Sexually active males or WOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of Abilify MyCite. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide.
3.	Any subject who participated in another clinical trial within 30 days of enrollment into the current trial.
4.	Subjects who are currently being treated with an LAI antipsychotic or have been treated with an LAI in the retrospective 6-month phase.
5.	Subjects with a current DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, bipolar I disorder, MDD, delirium, dementia, amnesic, or other cognitive disorders. Also, subjects with borderline, paranoid, histrionic, or antisocial personality disorder.
6.	Subject with any disorder including but not limited to intellectual developmental delay or disorder, major neurocognitive disorder or other condition that may impact the subject's ability to participate in the trial or interact with the smartphone application.
7.	Subject who is likely to be incapable of using the Abilify MyCite technology, even with assistance.

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Table 3.4.3-1 Exclusion Criteria	
8.	Subject who has a history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere with assessments of safety or usability during the course of the trial, including but not limited to, hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the investigator.
9.	Subject with a known allergy to adhesive tape or any pertinent components of the patch or aripiprazole tablet embedded with an IEM sensor (Abilify MyCite).
10.	Any subject who, in the opinion of the investigator or the medical monitor, should not participate in the trial.

LAI = long-acting injectable; WOCBP = women of childbearing potential.

Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal for at least 12 consecutive months.

Subjects must agree to restrictions to medications as described in [Section 4](#).

3.5 Endpoints

3.5.1 Primary Endpoint

The primary endpoint is the comparison of inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization) between the retrospective period (Month 1 to 3) while subjects are on oral standard-of-care antipsychotic treatment and the prospective period (Month 1 to 3) after the subjects switch to Abilify MyCite.

3.5.2 Secondary Endpoint

Improved adherence based on overall PDC with Abilify MyCite versus retrospective oral atypical antipsychotics.

3.5.3 Exploratory Endpoints

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

3.5.4 Safety Endpoints

Adverse events will be examined by frequency, severity, seriousness, and discontinuation (all cause and due to AEs). The safety and tolerability of Abilify MyCite, as assessed by the frequency and severity of SAEs, device-related nonserious AEs, potential hepatotoxicity cases, and pregnancies will be assessed along with an evaluation of any product quality complaints that arise. The Columbia Suicide Severity Rating Scale (C-SSRS) will be completed at baseline and all subsequent visits to assess the risk of suicide events and to classify reported suicide events.

3.6 Measures to Minimize/Avoid Bias

This trial is open-label.

3.7 Trial Procedures

The duration of this trial from first subject enrolled to first subject completed is estimated to be up to approximately 8.5 months including a 45-day screening period and a 6-month prospective phase that includes a required 3 months (Months 1 to 3) of Abilify MyCite

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treatment. This will be followed, at investigator discretion, to either change to standard-of-care antipsychotic treatment (eg, oral or LAI) or remain on Abilify MyCite for the second 3-month period (Months 4 to 6), during the prospective phase. The final trial visit will be on Month 6/ET and will be followed by a 30-day (\pm 3 day) safety follow-up period for subjects continuing on Abilify MyCite. For subjects completing Months 4 to 6 on standard of care, a 30-day safety follow-up period is not required. Total length of participation in the trial will vary depending on the screening duration and if the subjects remain on Abilify MyCite treatment.

At the screening visit, informed consent will be obtained before any trial-related assessments or procedures are performed. Initiation of the Abilify MyCite treatment will commence at the baseline visit (Day 1) for the subjects who meet all applicable eligibility criteria (Section 3.4), based on a series of assessments conducted at the screening visit. The first dose of Abilify MyCite is to be taken at the baseline (Day 1) visit (in the clinic) during onboarding, unless they have already taken their daily dose. Subjects should not take their oral standard-of-care medication that morning before the baseline visit.

During screening visit, the investigator will provide training on the correct use and required procedures associated with Abilify MyCite. The subject will be provided with patches, aripiprazole tablet embedded with an IEM sensor (Abilify MyCite) product, other supplies, and instructions on the procedures to be followed over the coming weeks.

Subjects will be monitored on the technology by the investigators, who can review the physician dashboard data and make changes to current treatment plan and therapy at their discretion. The investigators may request that a subject return to the site for unscheduled visits as deemed appropriate. In the event of an unscheduled visit, data collected will be at the investigator discretion per allowed data collection points noted in the schedule of assessments (Table 3.7-1). By Day 14 of the trial, if it is the opinion of the investigator that it is not appropriate for a subject to continue using Abilify MyCite, then the subject may be discontinued from trial participation but will be followed on oral atypical antipsychotic medication through the Month 6/ET visit.

Subjects will also visit the clinic for dispensing patches, Abilify MyCite product, and other supplies at Months 1, 2, 4, and 5. Any treatment changes, including reason for the change, will be recorded in the eCRF. Additionally, clinical evaluations will occur at Month 3 visit.

At the Month 6/ET visit, designated assessments and procedures will be conducted. The Month 6/ET visit marks the end of the assessment period. The subject will stop taking

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Abilify MyCite product and will restart his/her standard-of-care treatment (routine follow-up from care teams). All trial materials will be returned to the trial site.

For subjects continuing on Abilify MyCite, a follow-up telephone contact will be made 30 days (\pm 3 days) after the last dose of aripiprazole tablet embedded with an IEM sensor (Abilify MyCite) product (for subjects who withdraw early and for those who complete the trial). The Month 6/ET visit will serve as the final safety visit for subjects who complete the study on standard-of-care treatment.

Trial assessment time points are summarized in [Table 3.7-1](#).

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Table 3.7-1 Schedule of Assessments										
Assessments	Screening Days -45 to -1	Prospective Phase (Day 1 to Month 6/ET)^a							Follow -Up^b	Notes
		Abilify MyCite treatment required (Months 1 to 3)			Abilify MyCite or PRN oral atypical antipsychotic treatment (Months 4 to 6)					
		Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6/ET	Month 7	
		Day 1	- 3/+ 2 days			- 3/+ 2 days			± 3 days	
Record retrospective hospitalization and intervention data per protocol	X ^c									
Informed consent	X									Section 3.4.1
Inclusion/exclusion criteria	X									Section 3.4
Demographic information	X									
Psychiatric history	X									
Urine pregnancy test (WOCBP) ^d	X	X								Section 3.7.3.2
Confirmation of diagnosis of schizophrenia by DSM-5	X									
C-SSRS (Baseline/Screening Version)	X									Section 3.7.3.5
C-SSRS (Since Last Visit Version)		X			X			X		Section 3.7.3.5
ECG collection	X									Section 3.7.3.4
Vital signs	X	X			X			X		Section 3.7.3.3
Adverse events	X	X			X			X	X	Section 5
Discontinue prohibited medications	X									Section 4
Smartphone verification	X									
Onsite onboarding with Abilify MyCite; subject pairs/applies patch		X								Section 3.2.2.2
Dispense aripiprazole tablet embedded with an IEM sensor (Abilify MyCite), patches, and other supplies		X	X	X	X	X ^e	X ^e			
Review Abilify MyCite dashboard data every 2 weeks		X	--X ^f --			--X ^f --			--X ^f --	

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Table 3.7-1 Schedule of Assessments										
Assessments	Screening	Prospective Phase (Day 1 to Month 6/ET)^a							Follow-Up^b	Notes
		Baseline	Abilify MyCite treatment required (Months 1 to 3)			Abilify MyCite or PRN oral atypical antipsychotic treatment (Months 4 to 6)				
		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6/ET	Month 7		
		Day 1	- 3/ + 2 days			- 3/ + 2 days			± 3 days	
Accountability for aripiprazole tablet embedded with an IEM sensor (Abilify MyCite), patches, and other supplies			X	X	X	X ^e	X ^e	X ^e		
Healthcare utilization record evaluation					X			X		Section 3.7.1.4
Subject usability and satisfaction scale					X			X ^g		Section 3.7.2.1.8
Follow-up phone call									X	

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- ^a Monthly assessments will follow a 28-day schedule.
- ^b A follow-up phone call for subjects who conclude the study on Abilify MyCite will occur 30 days (\pm 3 days) after the Month 6/ET visit.
- ^c Retrospective hospitalization and intervention data will be collected only after trial eligibility is confirmed. This includes all psychiatric interventions (ie, hospitalizations, emergency department visits, partial hospitalization visits, intensive outpatient visits, assertive community treatment visits, outpatient visits for psychotherapy and/or medication management, etc.).
- ^d Urine pregnancy tests may be repeated if the investigator suspects that a subject is pregnant.
- ^e Abilify MyCite components (aripiprazole tablet embedded with an IEM sensor [Abilify MyCite], patches, and other supplies) will be dispensed and accountability performed only if subjects remain on Abilify MyCite treatment during Months 4 to 6 of the prospective phase. Any treatment changes, including reason for the change, will be recorded in the eCRF.
- ^f The trial physician is expected to regularly review the Abilify MyCite dashboard data during active Abilify MyCite use as consistent with routine care, approximately every 2 weeks. Note that "--x--" indicates an activity that occurs multiple times during the period.
- ^g Scales will be administered at the Month 6/ET visit for subjects who used Abilify MyCite during Months 4 to 6.

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3.7.1 Schedule of Assessments

3.7.1.1 Retrospective Phase (6 Months)

Subjects must have been prescribed oral antipsychotic standard-of-care pharmacotherapy for at least 6 months or longer, with evidence of prescription (ie, pharmacy records), during the retrospective phase and prior to screening. Subjects administered antipsychotics other than aripiprazole may cross-titrate onto oral aripiprazole during the screening period at the discretion of the investigator to be eligible for trial participation.

All hospitalizations and all interventions (psychiatric only) will be recorded in the source documentation.

3.7.1.2 Screening Visit

Eligible subjects will come to the trial site, on a day agreed upon by the subject (and his or her caregiver/support person, if applicable) and the investigator, to undergo screening assessments.

At the screening visit, the following will be performed:

- Retrospective hospitalization and intervention data will be collected only after trial eligibility is confirmed.
- Informed consent ([Section 3.4.1](#)).
 - The subject must provide documented informed consent before any other trial assessments or procedures are performed.
 - If the subject has a caregiver/support person, that caregiver/support person also must provide written informed consent.
- Eligibility Assessment ([Section 3.4](#)).
 - All protocol inclusion and exclusion criteria will be reviewed by the investigator; only subjects who meet all of the inclusion criteria and none of exclusion criteria may be considered for further participation in the trial.
- Obtain demographic information and psychiatric history.
- Obtain urine sample for pregnancy test (women of childbearing potential [[WOCBP](#)]; [Section 3.7.3.2](#)).
- Confirm diagnosis of schizophrenia by DSM-5.
- Administer the suicidality assessment (C-SSRS baseline version; [Section 3.7.3.5](#)).
- Perform electrocardiogram (ECG) collection ([Section 3.7.3.4](#)).
- Perform vital signs assessment ([Section 3.7.3.3](#)).
- Monitor AEs, including device-related nonserious AEs ([Section 5](#)).
- Discontinue prohibited medications ([Section 4](#)).

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- Smartphone verification: Each subject will be asked to confirm the availability of a suitable smartphone for the trial, in addition to confirming a wireless local area networking (wireless fidelity [Wi-Fi]) connectivity option is available to them. A subject with a smartphone that is not compatible with the Abilify MyCite app will be offered a loaner phone for the trial period.
- [REDACTED] (Section 3.7.2.1.2).

3.7.1.3 Prospective Phase (6 Months)

The prospective phase is 6 months from the baseline visit (Day 1) to the Month 6/ET visit. Subjects will have their final assessment visit at Month 6/ET. Monthly assessments will follow a 28-day schedule.

In the event a scheduled assessment period visit is missed by a subject, the trial site will contact the subject immediately and reschedule another visit as close to the original visit schedule date as possible. After at least 2 phone calls are attempted, a certified letter will be sent to the subject. If a rescheduled visit falls outside of the allowable time window, then the investigator will contact the sponsor (or designee) to determine whether the subject can continue in the trial and to obtain approval to continue or discontinue the subject.

3.7.1.3.1 Baseline (Day 1)

After completion of the screening visit assessments and procedures, the subject will return for the baseline visit.

At the baseline visit, the following will be performed:

- Obtain urine sample for pregnancy test (WOCBP; Section 3.7.3.2).
- Administer the suicidality assessment (C-SSRS Since Last Visit Version; Section 3.7.3.5).
- Perform vital signs assessment (Section 3.7.3.3).
- Monitor AEs, including device-related nonserious AEs (Section 5).
- Abilify MyCite system onboarding (Section 3.2.2.2).
- The following will be dispensed to the subject:
 - Abilify MyCite products (aripiprazole tablet embedded with an IEM sensor), supplies, and patches (prescribed dose is recorded) sufficient for 1 month (from baseline [Day 1] to Month 1).
 - Instructions on how to install the Abilify MyCite smartphone application.
 - User Guide for Abilify MyCite including introductory video and reference guides.
 - Contact information for the call center.

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- The first dose of Abilify MyCite is to be taken at the baseline (Day 1) visit (in the clinic) during onboarding, unless they have already taken their daily dose. Subjects should not take their oral standard-of-care medication that morning before the baseline visit.
- Review subject and investigator dashboards with the subject.
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

3.7.1.3.2 Months 1 and 2 Visits

At the Months 1 and 2 visits (- 3/ + 2 days), the following will be performed:

- Abilify MyCite products (aripiprazole tablet embedded with an IEM sensor), supplies, and patches (prescribed dose is recorded) sufficient for 1 month will be dispensed. Any treatment changes, including reason for the change, will be recorded in the eCRF.
- Accountability of patches and Abilify MyCite product (aripiprazole tablet embedded with an IEM sensor) supplies performed.
- Review Abilify MyCite dashboard data every 2 weeks.
- [REDACTED]

3.7.1.3.3 Month 3 Visit

Month 3 (- 3/ + 2 days) will be an investigator visit for the subject. At the Month 3 visit, the following will be performed:

- Administer the suicidality assessment (C-SSRS Since Last Visit Version; [Section 3.7.3.5](#)).
- Perform vital signs assessment ([Section 3.7.3.3](#)).
- Monitor AEs, including device-related nonserious AEs ([Section 5](#)).
- Abilify MyCite products (aripiprazole tablet embedded with an IEM sensor), supplies, and patches (prescribed dose is recorded) sufficient for 1 month will be dispensed. Any treatment changes, including reason for the change, will be recorded in the eCRF.
- Accountability of patches and Abilify MyCite product (aripiprazole tablet embedded with an IEM sensor) supplies performed.

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- Review Abilify MyCite dashboard data every 2 weeks.
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Healthcare utilization record evaluation ([Section 3.7.1.4](#)).
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

3.7.1.3.4 Months 4 and 5 Visits

At the Months 4 and 5 visits (- 3/ + 2 days), the following will be performed for subjects remaining on Abilify MyCite treatment:

- Abilify MyCite products (aripiprazole tablet embedded with an IEM sensor), supplies, and patches (prescribed dose is recorded) sufficient for 1 month will be dispensed. Any treatment changes, including reason for the change, will be recorded in the eCRF.
- Accountability of patches and Abilify MyCite product (aripiprazole tablet embedded with an IEM sensor) supplies performed.
- Review Abilify MyCite dashboard data every 2 weeks.

3.7.1.3.5 Month 6/Early Termination Visit

Month 6/ET (- 3/ + 2 days) will be an investigator visit for the subject. In addition, Month 6/ET visit evaluations are to be completed for any subject withdrawn from the trial at any time (for any reason other than full withdrawal of the consent). At the Month 6/ET visit, the following will be performed:

- Administer the suicidality assessment (C-SSRS Since Last Visit Version; [Section 3.7.3.5](#)).
- Perform vital signs assessment ([Section 3.7.3.3](#)).
- Monitor AEs, including device-related nonserious AEs ([Section 5](#)).
- Accountability of patches and Abilify MyCite product (aripiprazole tablet embedded with an IEM sensor) supplies performed for subjects remaining on Abilify MyCite treatment. Any treatment changes, including reason for the change, will be recorded in the eCRF.
- Review Abilify MyCite dashboard data every 2 weeks for subjects remaining on Abilify MyCite treatment.

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- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Healthcare utilization record evaluation ([Section 3.7.1.4](#)).
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

3.7.1.4 Healthcare Utilization Record Evaluation (Month -6 Through Month 6/ET)

Healthcare utilization record evaluation will take place 6 months prior to and following the baseline (Day 1) visit (for a total of 12 months) to evaluate the subject health records and to examine subject interaction with the investigators prior to and following usage of Abilify MyCite. All hospital admissions and number of days spent in an inpatient setting (psychiatric) would be recorded and assessed as either ‘planned’ or ‘unplanned’ and ‘related’ or ‘unrelated’ to the psychiatric illness. Similarly, all encounters between any investigators (psychiatric) and the subject will be recorded to obtain the following information:

- The nature of the contact (eg, office visit, partial hospitalization).
- The investigator role (eg, community psychiatric nurse).
- Whether the contact was planned or not.
- Whether or not the contact was initiated as a result of data from Abilify MyCite.
- Any medication titration, adherence counseling, education, and lifestyle coaching.

Intervention data includes psychiatric hospitalizations, outpatient visits, the number of crisis interventions, and pharmacy cost of all medications. This data will be recorded in the eCRF at Month 3 and Month 6/ET.

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3.7.1.5 Follow-up

A follow-up phone call for subjects who conclude the study on Abilify MyCite will occur 30 days (\pm 3 days) after the Month 6/ET visit, which will be the last official subject contact. At this time, the investigator will review SAEs and device-related nonserious AEs and the subject and investigator dashboards with the subject.

3.7.2 Efficacy Assessments

Not applicable.

3.7.2.1 Other Trial Assessments

3.7.2.1.1 Hospitalization

Data on subject inpatient psychiatric hospitalizations and outpatient or non-inpatient psychiatric treatment visits will be continuously reported during the trial. This data will include number and mean duration of all other (non-inpatient) psychiatric treatment visits including, but not limited to hospitalizations, emergency department visits, partial hospitalization visits, intensive outpatient visits, assertive community treatment visits, outpatient visits for psychotherapy and/or medication management, etc.

This information will be captured on the eCRF.

[REDACTED]

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3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to [Section 5](#), Reporting of AEs.

3.7.3.2 Clinical Laboratory Assessments

Urine pregnancy for WOCBP will be conducted at screening and Day 1. If deemed appropriate, serum pregnancy test will be performed if positive urine screen is detected. Additional clinical laboratory assessments will be performed at screening and at the investigator's discretion to ensure safety of the subject but are not required as part of this trial.

3.7.3.3 Vital Signs

Vital signs will be performed at screening, baseline (Day 1), Month 3, Month 6/ET, and at the investigator's discretion at subsequent visits to ensure safety of the subject but are not required as part of this trial.

3.7.3.4 Electrocardiogram Assessments

Electrocardiograms will be collected by the subjects at screening to confirm eligibility. Electrocardiogram recordings will be obtained after the subject has been at rest for at least 5 minutes. All ECGs will be reviewed by the investigator to assess normal from abnormal results. Any screening ECG with abnormal result(s) considered to be clinically significant can be repeated to confirm the finding(s) prior to excluding the subject.

3.7.3.5 Suicidality

Suicidality will be monitored throughout the trial using the C-SSRS.²² The C-SSRS was developed by a team of researchers at Columbia University to address the need for standardized classification of suicide reports to assess suicide risk. This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicide events and suicidal ideation and a post-baseline evaluation that focuses on suicidality since the last assessment. The Baseline/Screening Version and the Since Last Visit version of the C-SSRS will be completed by trained trial site staff at the time points presented in the Schedule of Assessments [Table 3.7-1](#).

3.7.4 End of Trial

The end of trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up visit for the last subject completing or withdrawing from the trial.

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3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

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

3.8.2 Individual Site

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

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After enrollment, a subject may stop Abilify MyCite treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, device-related nonserious AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. For subjects who elect to discontinue early for any reason, the sponsor would like to follow the subject for the total trial duration to track healthcare utilization with and without use of Abilify MyCite.

By Day 14 of the trial, if it is the opinion of the investigator that it is not appropriate for a subject to continue using Abilify MyCite, then the subject may be discontinued from trial participation but will be followed on oral atypical antipsychotic medication through the Month 6/ET visit.

If any subject discontinues the trial early, every effort should be made to complete the Month 6/ET evaluations (see [Table 3.7-1](#)) at that visit. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone or investigator visit at 1 month (\pm 3 days) after the Month 6/ET visit.

3.8.3.2 Documenting Reasons for Treatment Discontinuation

A subject may discontinue Abilify MyCite for a number of reasons including those listed below:

- Reasons related to AE:

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- Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard.
- Continuing 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 Abilify MyCite).
 - SAE.
 - Other potentially Abilify MyCite-related safety concerns or AEs.
- Death.
- Reasons unrelated to medical condition (provide detail and review AE history with subject).
- Withdrawal of informed consent (complete written withdrawal of consent form).
- Lost to follow-up.
- Pregnancy (see [Section 5.5](#)).
- Termination of all or part of the trial by the sponsor.

If the subject discontinues Abilify MyCite due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

3.8.3.3 Withdrawal of Consent

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

Complete withdrawal of consent requires a subject's refusal of all of the following methods of follow-up (these methods of follow-up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol-specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.

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- 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. A subject may initially express their desire to discontinue Abilify MyCite administration, which is not equivalent to a complete withdrawal of consent for further participation (see [Section 3.8.3.1](#)). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in [Section 3.8.3.2](#) to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on trial treatment. For the purposes of this trial, Abilify MyCite treatment begins with the first administration of Abilify MyCite on Day 1 of the prospective phase. Subjects who sign an eICF but who are not started on treatment are permitted to be re-screened. In the event that the subject is re-screened for trial participation, and the re-screening is not completed within the original screening window, a new eICF must be signed.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually received all doses of Abilify MyCite. For the purposes of this trial, subjects who complete the Month 6/ET visit will be defined as treatment completers. Subjects who are

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evaluated at the last scheduled visit during the treatment period will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the last scheduled trial visit during the treatment period and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as “lost to follow-up” as the reason for discontinuation.

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.

3.12 Subject Compliance

Subjects will be required to have at least 3 months of Abilify MyCite medication. Noncompliant subjects will be followed throughout the trial period and analysis will be performed as described in [Section 7.4](#). Discontinuation of noncompliant subjects is at the discretion of the investigator.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, Abilify MyCite dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor 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 and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

The investigator may continue subjects on their stable/current mood stabilizer(s) or antidepressant dose (must be stable for at least 14-days prior to Abilify MyCite) to maintain clinical stability of the subjects during the trial. Other oral non-aripiprazole antipsychotic medications may be allowed if approved by the medical monitor and sponsor; however, clozapine will not be allowed. Nonoral formulations of these antipsychotic medications are also not allowed. The use of varenicline beyond the

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screening visit is not allowed. If a subject is receiving varenicline at the screening visit, attempts should be made to discontinue the medication, if clinically feasible, to allow potential subjects to enter the trial.

Subjects must stop all other prohibited concomitant medications prior to administration of Abilify MyCite and for the duration of the trial.

Subjects must wash out from the following prohibited concomitant medications/therapies for the time periods specified:

- Use of approved long-acting antipsychotics within 6 months prior to signing the ICF.

Inhibitors and inducers of cytochrome P450 (CYP)3A4 and inhibitors of CYP2D6 isozymes are not allowed within 14 days (with the exception of fluoxetine which needs to be discontinued at least 28 days prior) prior to administration of Abilify MyCite and for the duration of the trial, since these are the pathways in which aripiprazole is metabolized.

An example list of CYP3A4 and CYP2D6 inhibitors and CYP3A4 inducers prohibited during the trial is provided in [Table 4.1-1](#).

Table 4.1-1 Example List of CYP3A4 and CYP2D6 Inhibitors and CYP3A4 Inducers Prohibited During the Trial	
CYP3A4 Inhibitors	
Amiodarone	Fluvoxamine
Amprenavir	Indinavir
Aprepitant	Itraconazole
Chloramphenicol	Ketoconazole
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole (if used orally)	Quinupristin/Dalfopristin
Delavirdine	Ritonavir
Diltiazem	Saquinavir
Erythromycin	Troleandomycin
Fluconazole	Verapamil
CYP2D6 Inhibitors	
Celecoxib	Hydroxyzine
Chloroquine	Methadone
Chlorpheniramine	Moclobemide
Clemastine	Paroxetine
Clomipramine	Pyrilamine
Diphenhydramine	Quinidine
Fluoxetine	Terbinafine
Halofantrine	Tripeleminamine

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Table 4.1-1 Example List of CYP3A4 and CYP2D6 Inhibitors and CYP3A4 Inducers Prohibited During the Trial	
CYP3A4 Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Efavirenz	Rifampin
Nevirapine	St. John's wort
Phenobarbital	Troglitazone

Note: The above is not an exhaustive list and there may be additional CYP3A4 and CYP2D6 inhibitors and CYP3A4 inducers that are prohibited during the trial.

4.2 Restricted Medications

Use and washout of any other therapy (prescription medication, over-the-counter, herbal medication, or vitamins) not listed in [Section 4.1](#) must be approved by the sponsor and the medical monitor.

Benzodiazepine use is allowed up to a maximum of 6 mg/day lorazepam or equivalent, but not within 8 hours of any rating scales during the trial. The use of intramuscular lorazepam is also permitted for emergent agitation, but only if deemed absolutely necessary by the investigator. The following guide should be used to determine approximate lorazepam equivalents: 1 mg lorazepam; = 5 mg diazepam; = 15 mg oxazepam; = 15 mg clorazepate. Subjects must not be on more than one benzodiazepine beyond the screening visit.

If a subject is receiving 2 benzodiazepines at the screening visit (eg, lorazepam and oxazepam), attempts should be made to discontinue one of the benzodiazepines, if clinically warranted, to allow potential subjects to enter the trial. The second benzodiazepine should be tapered off over an appropriate amount of time within the 45-day screening period to prevent side effects, and the subject should be maintained on the remaining benzodiazepine for at least 14 days prior to the administration of Abilify MyCite. Benzodiazepine use is allowed during the trial to manage AEs such as agitation, anxiety, and insomnia; however, non-benzodiazepine sleep aids are recommended for insomnia. Combined use of both drug classes (ie, benzodiazepines and non-benzodiazepine sleep aids) as treatment for insomnia is not allowed. Benzodiazepine use should be discontinued as soon as the AE for which it was initiated subsides, as per the investigator's discretion to avoid any withdrawal effects.

Medications that are restricted during the trial are listed in [Table 4.2-1](#).

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Table 4.2-1 Medications Restricted During the Trial		
Medication	Screening	Treatment Period
Anticholinergics ^a	≤ 4 mg/day benztropine or equivalent	≤ 4 mg/day benztropine or equivalent
Propranolol (for akathisia or tremor) ^{b, c}	Maximum 60 mg propranolol per day	Maximum 60 mg propranolol per day
Benzodiazepines ^b	-	No more than one benzodiazepine and not in combination with other sleep aid medication

^aAnticholinergics are not allowed within 12 hours of any rating scales during any phase of the trial.

^bIs not allowed within 8 hours of any rating scales during any phase of the trial.

^cSubjects receiving propranolol for heart disease may remain on stable, pretrial doses, as needed, throughout the trial, so long as the total dose does not exceed 60 mg/day.

5 Reporting of Adverse Events

The following describes the methods and timing for assessing, recording, and analyzing safety parameters, as well as the procedures for eliciting reports of and recording and reporting AEs and intercurrent illnesses and the type and duration of the follow-up of subjects after AEs.

5.1 Definitions

An AE is defined as any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as psychiatric history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to Abilify MyCite related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that Abilify MyCite caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between Abilify MyCite and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

An SAE includes any event that results in any of the following outcomes:

- Death.
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

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- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
 - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
 - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

A device-related SAE includes any event that results in any of the following outcomes:

- An event that reasonably suggests that a device has or may have caused or contributed to a death or serious injury.
 - Contributed to is defined as a death or serious injury that was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of any of the following:
 - Failure.
 - Malfunction.
 - Improper or inadequate design.
 - Manufacture.
 - Labeling.
 - User error.
- Serious injury means an injury or illness that includes any of the following:
 - Is life-threatening.
 - Results in permanent impairment of a body function or permanent damage to a body structure.
 - Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.
- Any of the following events that manufacturers or importers become aware of that reasonably suggests that one of their marketed devices:

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- May have caused or contributed to a death or serious injury.
- Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

For the purpose of this trial, device-related SAEs include any event that is related to the IEM, patch, or the phone and app (reported to Otsuka).

If an AE is related to the patch, then the skin irritation scoring system will be completed by the investigator. Patch-related AEs Grade 2 or above will be considered medically significant for purposes of this trial.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Device-related nonserious AEs are considered skin reactions caused by patch graded lower than Grade 2.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Any nonserious AE related to the Abilify MyCite Patch.
- Potential serious hepatotoxicity (see [Section 5.4](#)).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate Abilify MyCite discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication.

Severity: AEs will be graded on a 3-point scale and reported as indicated on the eCRF.

The intensity 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 Abilify MyCite is defined as follows:

- Related:** There is a reasonable possibility of a temporal and causal relationship between Abilify MyCite and the AE.

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Not Related: There is no temporal or causal relationship between Abilify MyCite and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs from the time the eICF is signed until the end of the trial. For this trial, information on AEs will be followed for up to 7 months (including the safety follow-up period) after the first dose of Abilify MyCite has been administered. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: “How have you felt since your last visit?” All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRFs provided by the sponsor. Serious AE collection is to begin after a subject has signed the eICF.

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

In addition, the sponsor must be notified immediately by telephone, fax, or email of any IREs according to the procedure outlined below, in [Section 5.3](#). Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, potential serious hepatotoxicity, or confirmed pregnancy, by telephone, fax, or email to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by email, fax, or overnight courier to the sponsor (please note that the IRE form is NOT the AE eCRF).

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject’s status to the sponsor.

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5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eCRF.

5.5 Pregnancy

Women of childbearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double barrier method) to prevent pregnancy during the course of the trial and for 30 days after the last dose of Abilify MyCite. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information.
- ICF.
- Pregnancy prevention information.
- Drug interactions with hormonal contraceptives.
- Contraceptives in current use.
- Guidelines for the follow-up of a reported pregnancy.

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with her.

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A urine and/or serum pregnancy test for human chorionic gonadotropin will be performed at screening and Day 1 on all WOCBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives Abilify MyCite, the Abilify MyCite administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive Abilify MyCite and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking Abilify MyCite, it must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, Abilify MyCite will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. [Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the Clinical Safety and Pharmacovigilance department (see the cover page of this protocol for contact information).]

The investigator must immediately notify the sponsor of any pregnancy associated with Abilify MyCite exposure during the trial and for 30 days after the last dose of Abilify MyCite and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

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

5.6 Procedure for Breaking the Blind

Not applicable, this is an open-label trial.

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5.7 Follow-up of Adverse Events

5.7.1 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 on the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant psychiatric 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).

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

This trial requires that subjects be actively monitored for SAEs and IREs up to 1 month after the last dose of Abilify MyCite is administered.

Serious AEs and nonserious IREs that are identified or ongoing at the last scheduled contact must be recorded as such on the AE eCRF page. If updated information (eg, resolved status) on SAE or 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, according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up or has died.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring after Last Scheduled Contact

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

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6 Pharmacokinetic Analysis

Not applicable, no pharmacokinetic assessments will be performed in this trial.

7 Statistical Analysis

7.1 Sample Size

The primary endpoint of this trial compares the paired proportions of inpatient psychiatric hospitalization during the retrospective period (Month 1 to 3) and the prospective period (Month 1 to 3), which will be analyzed using a McNemar test.

Based on published results of other similar studies for the particular time periods (retrospective Month 1 to 3 and prospective Month 1 to 3)^{23,24} we are evaluating, it is reasonable to assume that 15.5% of subjects are hospitalized during retrospective Month 1 to 3 and 7% are hospitalized during prospective Month 1 to 3; about 5% of subjects who are not hospitalized retrospective will be hospitalized prospective, while 13.5% of subjects who are hospitalized retrospective will not be hospitalized. With this assumption, 200 completed subjects will provide 80% power (alpha = 0.05 two-sided) to detect a difference of 8.5% in 2 paired hospitalization proportions between pre-switch and post-switch periods while the proportion of total discordant pairs is 18.5%. In addition, this sample size will provide 80% power for the comparison of retrospective Month 4 to 6 vs prospective Month 4 to 6, assuming 30% of the subjects are hospitalized pre-switch (12.5% subjects will be hospitalized post-switch and another 17.5% won't have hospitalization post-switch) and, overall, 20% are hospitalized post-switch (among them, 12.5% subjects are hospitalized both pre-switch and post-switch and 7.5% have no hospitalization pre-switch).

Two interim analyses are planned at when 50% and 70% of subjects have completed the prospective period (Month 1 to 3); in order to conserve the overall Type I error at 0.05 level, 224 to 300 evaluable subjects are needed to complete the 3-month treatment to maintain 80% power. This sample size assumes the 3 sequential tests are made using LanDeMets Spending Function²⁵ with O'Brien-Fleming boundary, a futility conditional power of 15% is built in the sample size calculation to allow the trial to stop for futility. Based on the conditional power and the alpha level at the interim analysis, the trial could stop for efficacy or futility, continue with initially planned 224 sample size or increase to up to 300 if the conditional power fall between 30% to 80% (Section 7.4.4). The 2-sided alpha levels for these 2 interim analyses are 0.00312 and 0.0139 respectively, and the alpha left for the final analysis will be 0.04528.

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7.2 Datasets for Analysis

The safety dataset includes all subjects that were administered at least one dose of Abilify MyCite.

The following analysis samples are defined for this trial:

- Enrolled Sample: comprises all subjects who sign an eICF for the trial.
- Prospective Safety Sample: comprises all subjects who receive at least one dose of Abilify MyCite in the prospective phase.
- Efficacy Sample: the core dataset for all efficacy analyses is the modified Intent-to-Treat (mITT) dataset which will consist of data from all subjects entering the prospective phase who have completed the first 3-months of dosing on Abilify MyCite. However, as will be described below, in order to handle missing data and restrictions imposed by different types of analyses (eg, change from baseline analysis), other datasets derived from the ITT dataset will be used for the efficacy analyses.

7.3 Handling of Missing Data

For the primary variable, the analysis will be based on the proportion of days with good patch coverage during the trial and no imputation will be performed for missing data. For analysis of change from baseline (Day 1), last-observation-carried-forward (LOCF) and observed-cases (OC) methods will be used, as considered applicable. No imputation will be performed for other missing data, unless specified otherwise.

7.4 Primary and Secondary Endpoint Analyses

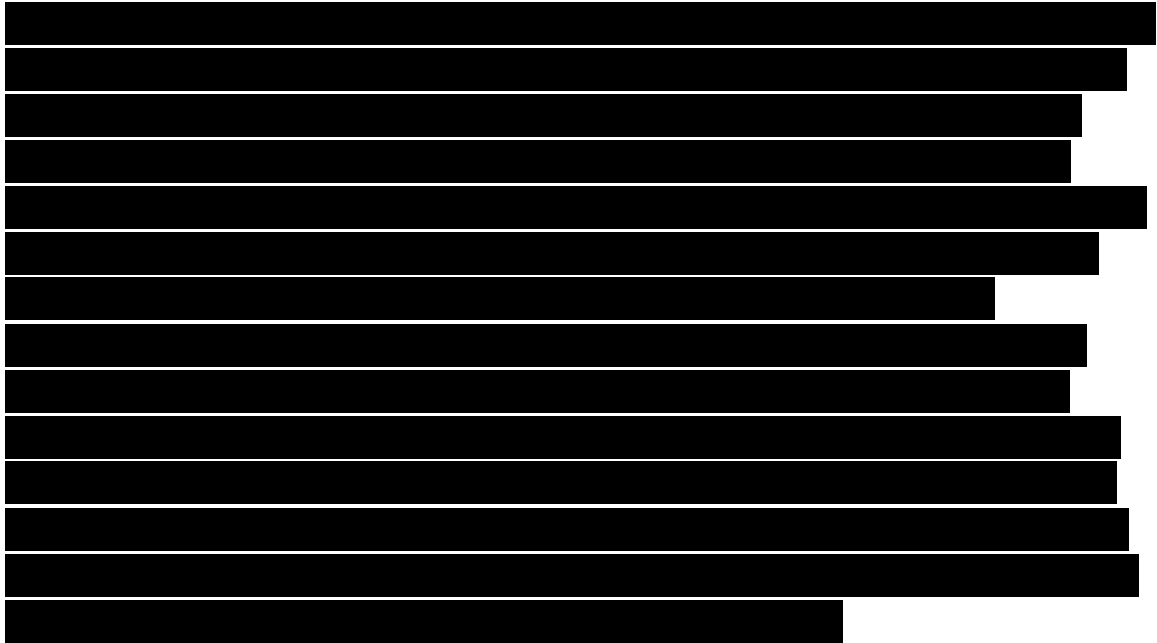
7.4.1 Primary Endpoint Analysis

The primary endpoint of this trial is the comparison of inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization[s]) between the retrospective period (Months 1 to 3) while on oral standard-of-care antipsychotic treatment and the prospective period (Months 1 to 3) after the switch to Abilify MyCite. This will be achieved by testing for statistically significant (at 2-sided overall alpha = 0.05). The analysis will be performed using a McNemar test on those who have hospitalization data during Months 1 to 3 prior to the screening period and during Months 1 to 3 after switch to Abilify MyCite.

7.4.2 Secondary Endpoint Analysis

The secondary endpoint is:

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7.4.4 Interim Analysis

Two interim analysis are planned when 50% and 70% of subjects have completed the prospective phase (3 months). At the end of the interim analysis, a decision will be made to continue with/without sample size increase, stop for efficacy or stop for fertility based on the p-value and conditional power from the interim data (as described in [Table 7.4.4-1](#)). Subjects will continue to be enrolled into the trial during the interim analysis; if the trial is stopped due to futility, all randomized subjects will be terminated; however, if the interim analysis stops the trial for efficacy, then all randomized subjects will continue until the last observation. Subjects in screening will be discontinued and no further randomization will occur. The 2-sided alpha levels for these 2 interim analyses are 0.00312 and 0.0139 respectively, and the alpha left for the final analysis will be 0.04528. The sample size will be re-estimated only based on the conditional power determined at the interim analysis. The adaptive designs methodology published by Chen, Dements and Lan (2004)²⁶ will be used to increase the sample size based on the estimate of the treatment effect size of the primary efficacy endpoint at interim, possibly combined with other external information, without inflating the Type I error. Should the timing or frequency of the interim analysis be different from the previously specified, stopping boundary would be re-calculated using the alpha spending function.

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The Interim Analysis Plan and the statistical analysis plan will be developed to document the details of data flow, statistical methods and other logistical considerations relating to the interim analyses. Based on the interim analysis results, the trial sample size will be adjusted according to [Table 7.4.4-1](#).

Interim Results	Interim Analysis Recommendation	Sample Size (completers)
P – value less than specified alpha level at interim	Stop for efficacy	About 100 or 157
Conditional power \geq 80%	No adaption to the planned sample size	224
Conditional power \geq 30% and $<$ 80%	Increase sample size up to 300	300
Conditional power \geq 15% and $<$ 30%	No adaption to the planned sample size	224
Conditional power $<$ 15%	Stop the trial for futility	About 100 or 157

7.5 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, gender, weight, height and body mass index will be summarized by descriptive statistics (frequency, mean, median, SD, maximum, minimum, and percentage when applicable).

Baseline disease severity and psychiatric history will be also be summarized by descriptive statistics.

7.6 Safety Analysis

In general, baseline measurements of safety variables are defined as the last measurements prior to the first dosing of Abilify MyCite for the prospective phase of the trial. All safety summaries will be descriptive in nature.

7.6.1 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:

- Treatment-emergent AEs (TEAEs).
- TEAEs by severity.
- TEAEs potentially causally related to Abilify MyCite.
- Device-related TEAEs.
- TEAEs with an outcome of death.

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- Serious TEAEs.
- TEAEs leading to discontinuation of Abilify MyCite.

7.6.2 Clinical Laboratory Data

The urine pregnancy test and confirmatory serum test (if applicable) at screening on all WOCBP will be provided in a listing.

7.6.3 Vital Signs Data

Vital sign data (observed and change from baseline data) and the incidence of potentially clinically relevant vital signs will be summarized. Vital sign data will be presented in a listing.

7.6.4 Electrocardiogram Data

Electrocardiogram data will be presented in a listing.

7.6.5 Suicidality Assessment

The suicidality assessment data will be analyzed for evidence of any treatment-emergent issues related to suicidal ideation or behavior.

8 Management of Investigational Medicinal Product

8.1 Packaging and Labeling

Abilify MyCite will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The aripiprazole tablet embedded with an IEM sensor (Abilify MyCite) products will be supplied in bottles.

Each bottle used in the dosing period will be labeled to clearly disclose the subject identification (ID), compound ID, trial number, sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information as required by local regulatory authorities.

8.2 Storage

The aripiprazole tablet embedded with an IEM sensor (Abilify MyCite) products and patches will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide medical device to any subject not participating in this protocol.

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The medical device should be stored with, and in the same conditions as, the aripiprazole tablets embedded with an IEM sensor. The investigator or designee will maintain a temperature log in the storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator or designee must maintain an inventory record of Abilify MyCite (patches and aripiprazole tablet embedded with an IEM sensor) received, dispensed, administered, and returned. Any treatment changes, including reason for the change, will be recorded in the eCRF.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used aripiprazole tablets embedded with an IEM sensor (Abilify MyCite) products and patches must be destroyed at the trial site(s). The assigned investigator or designee will facilitate the destruction of unused and/or partially used aripiprazole tablets embedded with an IEM sensor (Abilify MyCite) products and patches.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications.
- Incorrect or missing labeling.
- Packaging issues (eg, damaged, dirty, crushed, missing product).
- Bottle defects (eg, under/over-fill, no safety seal).
- Vial defects.
- Product defect (eg, odor, chipped, broken, embossing illegible).
- Loss or theft of product.

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8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQC's identified through any means from the receipt of Abilify MyCite 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) by telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Phone - Abilify MyCite dedicated team at [REDACTED].

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

8.5.2 Information Required for Reporting Purposes

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

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

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

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQC's will be handled by the sponsor.

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9 Records Management

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

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

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents.
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to Abilify MyCite administration, and confirmation of the subject's actual participation in the trial.
- 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 Abilify MyCite must also be recorded.
- Any changes in concomitant medications or dosages.
- A general reference to the procedures completed.
- The signature (or initials) and date of all clinicians who made an entry in the progress notes.

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.

Source documents and source data will be captured electronically in this trial and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected

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into a system that is fully validated. Changes to the data will be captured by an automatic audit trail.

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

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

Another exception will be safety laboratory, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records will take place; however, on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess trial site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

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

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations.

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The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

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

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

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

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated 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 clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, Abilify MyCite supply, presence of required

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documents, the informed consent process, and comparison of case report forms (CRFs) with source documents. The investigator agrees to 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.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, ICH GCP Guideline (E6), 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 CRFs, the investigator, sub-investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code 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.

12 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 IMPs, subject bodily fluids, 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 numbers in CRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

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13 Amendment Policy

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). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of Abilify MyCite used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

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

14 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.

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

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

15 References

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Appendix 1 Names of Sponsor Personnel

[Redacted]
[Redacted] PhD

Phone: [Redacted]

Email: [Redacted]

[Redacted]
[Redacted]

Phone: [Redacted]

Email: [Redacted]

[Redacted]
[Redacted]

Phone: [Redacted]

[Redacted]

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Appendix 2 Safety Reporting

Report IREs (SAEs, confirmed pregnancies, and any device-related nonserious AEs [eg, skin irritation that is Grade 2 or worse]) to:

IQVIA Lifecycle Safety

Fax: [REDACTED]

Email: [REDACTED]

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Appendix 3 Abilify MyCite Contents

Abilify MyCite Contents	
Abilify MyCite Component	Description
Aripiprazole + IEM	Aripiprazole tablet with sensor will be dispensed to the subjects during the trial. Tablets will be taken as prescribed by the healthcare provider, with approximately 120 mL of water.
Patch	Patches will be dispensed to a subject for use. The current Abilify MyCite DW5 patch is a one-piece unit. The patch has an adhesive backing that adheres to the user's body and requires the patch to be changed approximately once per week. The updated patch (RW2) is made up of two parts; (1) a data pod and (2) an adhesive strip. As with the DW5 patch, the adhesive strip needs to be replaced approximately once per week, but the data pod is for extended use and needs to be inserted into the adhesive strip whenever it is changed. The updated patch was designed to eliminate the step of having to press a button to pair the patch with the app. The data pod only needs to be paired with the app on initial use and does so without the need to press a button, unlike the DW5 patch that needed to be paired with every application of a new patch. The new pod/strip combination also allows for an expanded area for patch placement.
Computing Device & Accessories	Subjects will use their own smartphone and required accessories. Subjects will be requested to carry their smartphone with them as much as possible and to plug in the device at a dedicated location at home where they could have easy and frequent access when not being carried. The preferred location is on a nightstand or a location immediately adjacent to where the subject sleeps.
Abilify MyCite Reference Guide	A printed reference guide will provide explicit directions for normal use and troubleshooting.

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Appendix 4 Protocol Amendment

Amendment Number: 1
Issue Date: 11 Feb 2019

PURPOSE:

The protocol was amended to revise the secondary and exploratory endpoints and to add an exploratory endpoint for the [REDACTED]. In addition, minor clarifications to the monthly assessments and corresponding trial days, assessment window, endpoints, inclusion and exclusion criteria, schedule of assessments, and ECG assessment language were incorporated.

BACKGROUND:

The intention of this protocol amendment was to revise the trial endpoints to better match the intended study objectives. These changes to clinical trial protocol 031-201-00301, issued 04 Jan 2019, are listed below in detail.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Description of Change	Sections Affected by Change
Clarified assessment window of - 3/ + 2 days for Months 1 through 6 globally	Global change
Clarified monthly assessments will follow a 28-day schedule and revised study days accordingly	Protocol synopsis Section 3.1 Type/Design of Trial Figure 3.1-1 Trial Design Schematic Section 3.5.3 Exploratory Endpoints Table 3.7-1 Schedule of Assessments Section 3.7.1.3 Prospective Phase (6 Months)
Clarified in the inclusion criteria that caregiver support may be utilized throughout the trial and that the caregiver/support person will be asked (where applicable) to provide feedback via the Caregiver Involvement Scale	Protocol synopsis Table 3.4.2-1 Inclusion Criteria
Removed exclusion criterion #4 regarding hospitalization during the screening period	Protocol synopsis Table 3.4.3-1 Exclusion Criteria
Clarified the secondary endpoint for the trial	Protocol synopsis Section 3.5.2 Secondary Endpoint Section 7.4.2 Secondary Endpoint Analysis
Revised several secondary endpoints to exploratory endpoints and clarified the exploratory endpoint analysis for the [REDACTED]	Protocol synopsis Section 3.5.3 Exploratory Endpoints Section 7.4.3 Exploratory Endpoint Analysis
Removed Abilify MyCite product, supplies, and patch dispensation at Month 6/ET	Table 3.7-1 Schedule of Assessments Section 3.7.1.3.5 Month 6/Early Termination Visit
Clarified language regarding ECG assessments	Section 3.7.3.4 Electrocardiogram Assessments

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ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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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 GCPs 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 IND, aripiprazole, 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 aripiprazole 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 case report forms 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 ICFs, 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 sub-investigators 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



This page is a manifestation of an electronically captured signature

SIGNATURE PAGE

Document Name: 031-201-00301 Protocol Amendment 1

Document Number: 1000021943

Document Version: 3.0

Signed by	Meaning of Signature	Server Date (dd-MMM- yyyy hh:min) - UTC timezone
[REDACTED]	Clinical Approval	11-Feb-2019 19:25:59
[REDACTED]	Biostatistics Approval	11-Feb-2019 17:03:20