- **Protocol number: 316-13-217**
- **Document title: A Multicenter, 180-day Pragmatic Clinical Trial to Measure the Difference in All-cause Hospitalizations for Patients Who Are Using Abilify MyCite Versus Virtual Matched Controls in Adults With Schizophrenia, Bipolar 1 Disorder, and Major Depressive Disorder**
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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Medical Device

Abilify MyCite (OPC-14597 Digital, aripiprazole tablet with sensor)

PROTOCOL

A Multicenter, 180-day Pragmatic Clinical Trial to Measure the Difference in All-cause Hospitalizations for Patients who are Using Abilify MyCite versus Virtual Matched Controls in Adults with Schizophrenia, Bipolar 1 Disorder, and Major Depressive Disorder

Protocol No. 316-13-217
NDA No. 207202

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	4
Study Type:	Pragmatic Clinical Trial
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Issue Date:	08 Mar 2018

Protocol Synopsis

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Product: Medical Device Abilify MyCite (OPC-14597 Digital; aripiprazole tablet with sensor)	Protocol No. 316-13-217
Protocol Title:	A Multicenter, 180-day Pragmatic Clinical Trial to Measure the Difference in All-cause Hospitalizations for Patients who are Using Abilify MyCite versus Virtual Matched Controls in Adults with Schizophrenia, Bipolar 1 Disorder, and Major Depressive Disorder
Clinical Development Phase:	4
Study Type:	Pragmatic Clinical Trial
Indication:	Adults with schizophrenia (SCH), bipolar 1 disorder (BP1), and major depressive disorder (MDD)
Objective(s):	The primary objective of this study is to assess the difference in all-cause hospitalizations between patients using Abilify MyCite versus virtual matched controls at Day 180. In addition, secondary and exploratory objectives will assess medication adherence, healthcare utilization and costs, and patient-reported outcomes.
Study Design/ Methodology:	**Main Study** This is a phase 4, open-label, prospective, pragmatic clinical trial to assess the difference between all-cause hospitalizations in patients using Abilify MyCite (for Months 1-3, then prohibited for Months 4-6) versus virtual matched controls from baseline to Day 180. Virtual matched controls CCI [redacted] would be receiving treatment as usual (ie, any product other than Abilify MyCite, which may be oral aripiprazole or any other product). Eligible patients will enter a screening period of up to 13 days. For patients enrolling into the study, those not on aripiprazole at screening will use the screening period for conversion to aripiprazole from other antipsychotics according to the approved labels. At the baseline visit (which may be the same visit as the screening visit), Abilify MyCite onboarding will be provided in the office, with commercial informational materials and additional call center support; then, patients will initiate 3 months of treatment with Abilify MyCite at the baseline visit.

During the following 3 months (Months 4-6), use of Abilify MyCite will be prohibited (and the patient continues with oral aripiprazole or other appropriate treatment, per routine clinical care). The primary endpoint will be assessed at Day 180.

After the visit at Day 180, a second, optional interventional period (up to 6 months of Abilify MyCite) may be initiated per the joint decision of the patients with their study physician; patients in this second, optional interventional period will have a visit at Day 360 (in addition to their regular visits as clinically indicated). During this second, optional interventional period, patients may start and stop Abilify MyCite as clinically indicated.

Enrolled patients will be matched to a virtual control group identified from CCI in a 1:3 ratio (enrolled patients on Abilify MyCite treatment versus virtual matched controls).

CCI the matching will be performed after the Abilify MyCite arm has been completed.

Exploratory Study

In addition, there will be a parallel exploratory study, which will utilize a different set of physicians and patients from the main study. Results from the exploratory study will be analyzed separately from the main study results.

Procedures for the exploratory study will be similar to those in the main study (see above), with the exception that there will be 1-month intervals of Abilify MyCite use (and 1-month intervals of prohibition of Abilify MyCite use). During periods of nonuse of Abilify MyCite, the patient continues with oral aripiprazole treatment, per routine clinical care.

In the exploratory study, each patient will receive Abilify MyCite per 1 one of 2 sequences over a 360-day period:

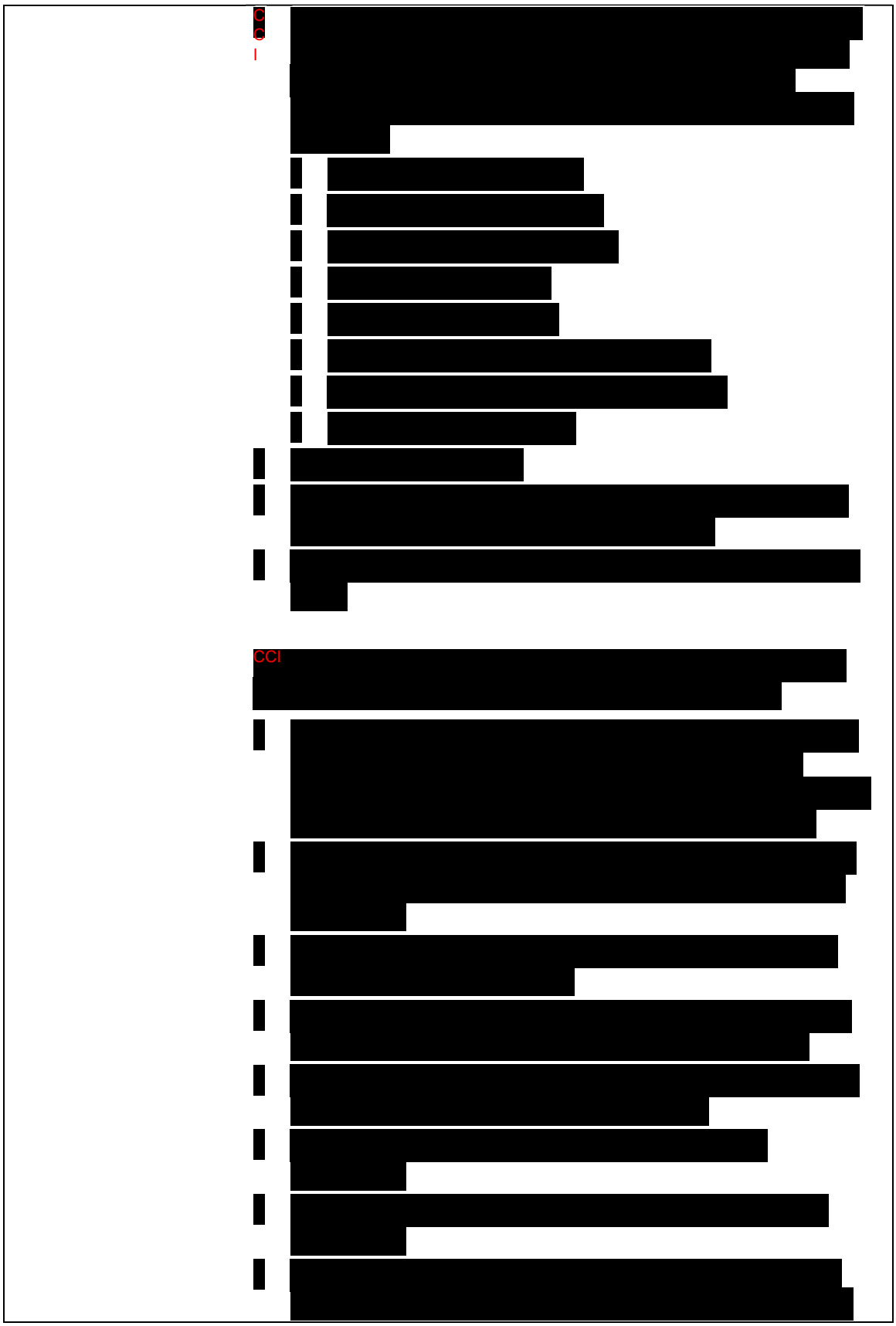
- **Sequence 1:** Only in Months 1, 2, 5, and 10.
- **Sequence 2:** Only in Months 1, 4, 7, and 10.

Sites will be randomized to 1 of the 2 sequences.

	For this exploratory study, the site visits will be at screening, baseline (which may be the same day as the screening visit), Day 180, and Day 360; additional visits are to occur as clinically indicated. The exploratory arm will begin after the main study is enrolled at approximately 50% (ie, staggered start).
Patient Population:	In both the main and exploratory studies, participants will be adult patients with SCH, BP1, or MDD who, within 60 days prior to study enrollment, had a hospitalization (all-cause or psychiatric, ie, for any reason) or at least 1 psychiatric partial hospital admission. To achieve balanced enrollment of the targeted diagnoses, a minimum enrollment of each diagnosis will be 25% for each study. The main study will enroll approximately 640 total patients. The exploratory study will enroll approximately 150 adult patients (75 per sequence), utilizing different sites from the main study (ie, a different set of patients and physicians).
Inclusion/Exclusion Criteria:	<u>Inclusion criteria</u> • Patients are actively enrolled in an Anthem-affiliated commercial, Medicaid, or Medicare health plan with medical and pharmacy benefits. • Male and female patients between the ages of 18 and 63 years, inclusive at the time of consent. • Patients must have a smartphone with data plan. • Patients must have a current diagnosis of SCH, BP1, or MDD. • Patients currently prescribed aripiprazole, or appropriate for aripiprazole treatment. • Within 60 days prior to study enrollment, patients are required to have had a hospitalization (all cause or psychiatric) or at least 1 psychiatric partial hospital admission. • Patients are deemed appropriate, per the study physician judgment, to use Abilify MyCite per the package insert and to enter this interventional study. • Patients must be able to read and understand English.

	Exclusion criteria • Any patient who participated in another clinical trial within 30 days of enrollment into the current study. • Females who are breast-feeding and/or who are pregnant at the time of study enrollment, or who plan to become pregnant during the study. • Patients who are currently being treated with a long-acting injectable antipsychotic.
Study Sites	Approximately 100 overall (main plus exploratory studies)
Device, Dose, Dosage Regimen, Treatment Period, Formulation, Mode of Administration:	Abilify MyCite® tracks drug ingestion and is composed of the following components: • Aripiprazole embedded with an ingestible event marker (IEM) sensor (Abilify MyCite); • MyCite® Patch (wearable sensor) that detects the signal from the IEM sensor after ingestion and transmits data to a smartphone; • MyCite App, a smartphone application (app), which is used with a compatible smartphone to display medication ingestion information for the patient; • Web-based portal or dashboard for healthcare providers (HCPs) and caregivers. The treatment medication dose decision will be determined by the study physicians independent from the protocol. Treatment period - Main Study Patients receive treatment with Abilify MyCite during Month 1 through Month 3. During Months 4 through 6, use of Abilify MyCite will be prohibited (and the patient continues with oral aripiprazole or other appropriate treatment, per routine clinical care). Thereafter, at Day 180, a second, optional interventional period (up to 6 months of Abilify MyCite) may be initiated per the joint decision of the patients with their study physician. Treatment period - Exploratory Study In the exploratory study, each patient will receive Abilify MyCite per 1 one of the 2 sequences over a 360-day period: • **Sequence 1:** Only in Months 1, 2, 5, and 10. • **Sequence 2:** Only in Months 1, 4, 7, and 10.

Study Assessments	CCI [redacted]
Criteria for Evaluation:	**Primary Endpoint (Main Study)** Difference in the proportion of patients with all-cause hospitalizations for patients using Abilify MyCite versus virtual matched controls from baseline to Day 180. **Secondary Endpoint (Main Study)** Difference between groups (Abilify MyCite versus virtual matched controls) in the proportion of patients with at least 80% proportion of days covered (PDC) (with antipsychotic medication) from baseline to Day 180. CCI [redacted]



	[redacted]
Statistical Methods:	For the main study, the primary analysis will be a comparison of proportions between the Abilify MyCite cohort and virtual matched control group based on standard formulas.
Study Duration:	The main study, the expected maximum study duration per patient from screening to their last visit will be 373 days (ie, up to 13 days screening, plus an expected maximum of 360 days in the study if the patient participates in the optional second interventional period). For the exploratory study, the expected maximum study duration per patient will be 373 days (ie, the same as the main study). Since the main and exploratory studies will utilize different physicians and patients, the expected maximum study duration for any patient will be 373 days.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
DILI	Drug-induced liver injury
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
FDA	United States Food and Drug Administration
FOCBP	Females of childbearing potential
HA	Alternative hypothesis
HCP	Healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
CCI	[redacted]
ICF	Informed consent form
ID	Identifier
IEC	Independent ethics committee
IEM	Ingestible event marker
IRB	Institutional review board
IRE	Immediately reportable event
MDD	Major depressive disorder
[redacted]	[redacted]
PDC	Proportion of days covered
[redacted]	[redacted]
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
SAE	Serious adverse event
SAP	Statistical analysis plan
SCH	Schizophrenia
Seq	Sequence
ULN	Upper limit of normal
US	United States

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 for[1]:

- Treatment of adults with schizophrenia (SCH);
- Treatment of bipolar 1 disorder (BP1):
  - 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 components[1]:

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

This trial will utilize commercially available Abilify MyCite.

The Abilify MyCite system has been tested in patients 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 patients and HCPs/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] CCI [redacted]

1.1 Rationale for Development of Abilify MyCite

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 patients, HCPs, and potentially caregivers. Abilify MyCite is intended to track drug ingestion and is indicated for the treatment of adults with SCH, BP1 (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 patient 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 patients 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 patients.

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

The Abilify MyCite system may be used by HCPs 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 HCPs 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 patients, 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 patient and HCP (and caregivers with patient 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 patient 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 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]

1.2 Components

CCI [redacted] an overview of the Abilify MyCite system is shown in Table 1.2-1.

CCI [redacted]

Also see Appendix 3 (Abilify MyCite Contents).

Table 1.2-1 Overview of Abilify MyCite System	
Characteristic	**Description**
Components	• Aripiprazole tablet embedded with an IEM sensor (Abilify MyCite) • MyCite Patch (wearable sensor) that detects the signal from the IEM sensor after ingestion and transmits data to a smartphone • MyCite App (a smartphone application [app] which is used with a compatible smartphone to display information for the patient) • Web-based portal for HCPs and caregivers
FDA-approved indication	• 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 SCH; treatment of BP1 (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.
Limitations of use	• The ability of Abilify MyCite to improve patient 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.

Also see Appendix 3 (Abilify MyCite Contents).

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 patient and to web-based software that can display information for an HCP or caregiver. The Abilify MyCite system is composed of the following components (Figure 1.2-1 and Table 1.2-1.)[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 MyCite Patch (wearable sensor) to track aripiprazole ingestion.
- 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 patient 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.
- MyCite App (a smartphone app which is used with a compatible smartphone to display information for the patient) to allow patients to review their medication ingestion as well as enter their behavioral data (patient rated mood and quality of

rest). These data can be shared with healthcare providers (HCPs) and caregivers with the patient's consent.

- Web-based portal for HCPs and caregivers provides an interface to review data shared by a patient.

2 Study Rationale and Objectives

2.1 Study 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 patients and consumers that may improve health management and medication compliance.[14] 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 patient's torso. The patch transmits data to the patient's mobile device (ie, smartphone), which uploads data to a secure, cloud-based server. Use of Abilify MyCite will allow patients to view their aripiprazole ingestion data on their mobile device; in this way, the patient can learn about their medication-ingestion patterns, which could enable greater patient awareness and self-management of their disease.

In addition, the patients' HCPs and elected caregivers can view data via a web-based portal served by the cloud-based server.[1] With Abilify MyCite tracking drug ingestion, all-cause hospitalizations (ie, hospitalizations for any reason) should be reduced when compared to virtual matched controls; this reduction is anticipated to be driven by an improvement in timely and appropriate treatment decisions based on objective data. CCI [redacted]

The main and exploratory studies will explore different use-patterns of Abilify MyCite to determine the durability of the system effect over time.

2.2 Study Objectives

The primary objective of this study is to assess the difference in all-cause hospitalizations between patients using Abilify MyCite versus virtual matched controls at Day 180.

In addition, secondary and exploratory objectives will assess medication adherence, CCI [redacted]

3 Study Design

3.1 Type/Design of Study

An overview of the main and exploratory studies is provided in Figure 3.1-1.

Study design schematics are provided in Figure 3.1-2 (main study) and in Figure 3.1-3 (exploratory study).

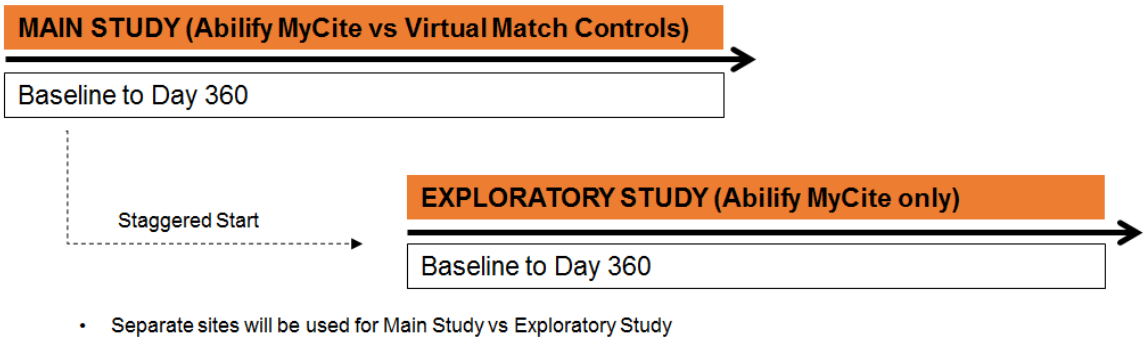


Figure 3.1-1 Overview of Pragmatic Study 316-13-217: Main Study and Exploratory Study

The exploratory arm will begin after the main study is enrolled at approximately 50% (ie, staggered start). Virtual matched controls [redacted] would be receiving treatment as usual (ie, any product other than Abilify MyCite, which may be oral aripiprazole or any other product).

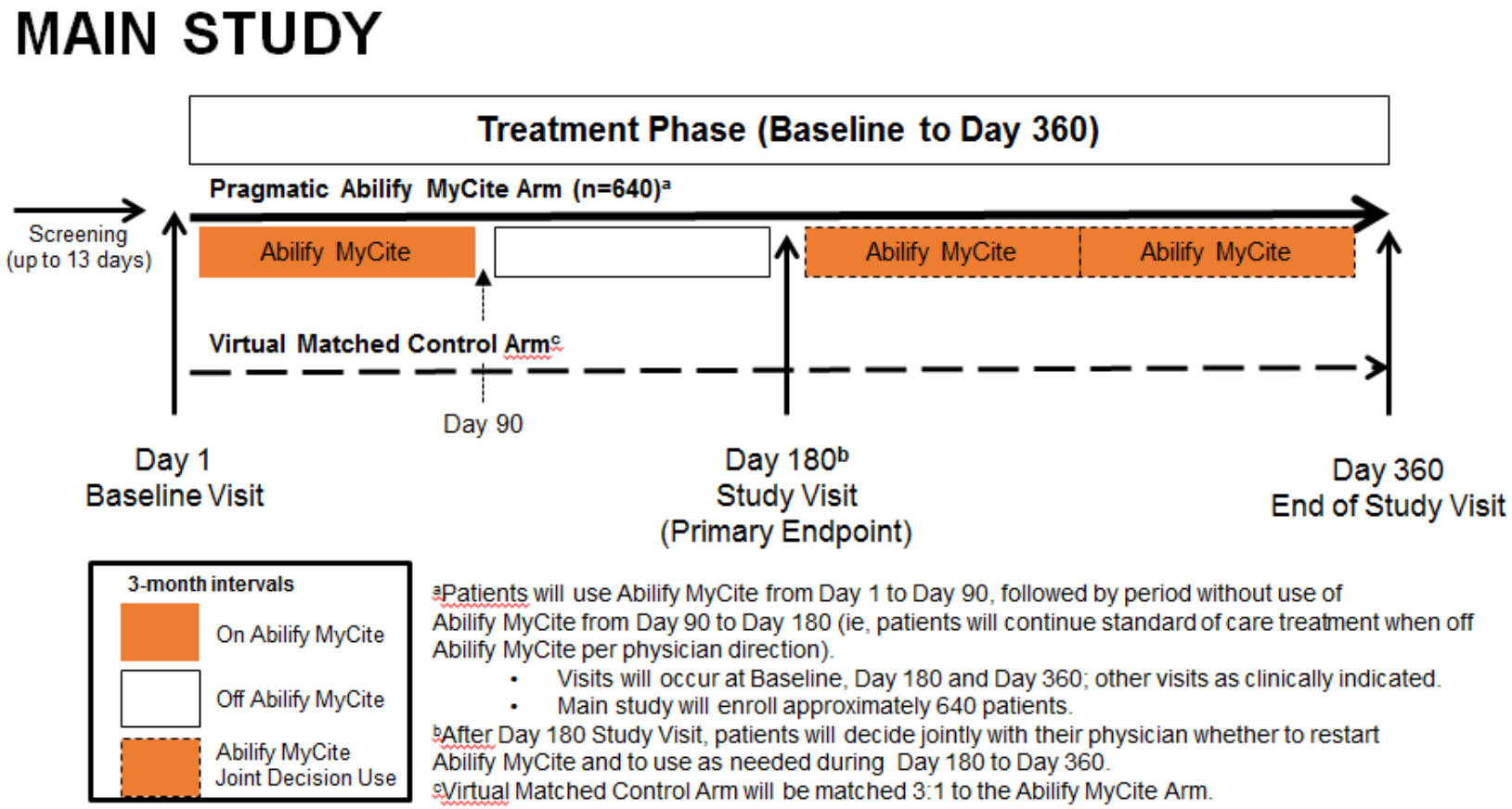


Figure 3.1-2 Study Design Schematic (Main Study)

The second, optional interventional period (up to 6 months of Abilify MyCite) may be initiated per the joint decision of the patients with their study physician. During this second, optional interventional period, patients may start and stop Abilify MyCite as clinically indicated.

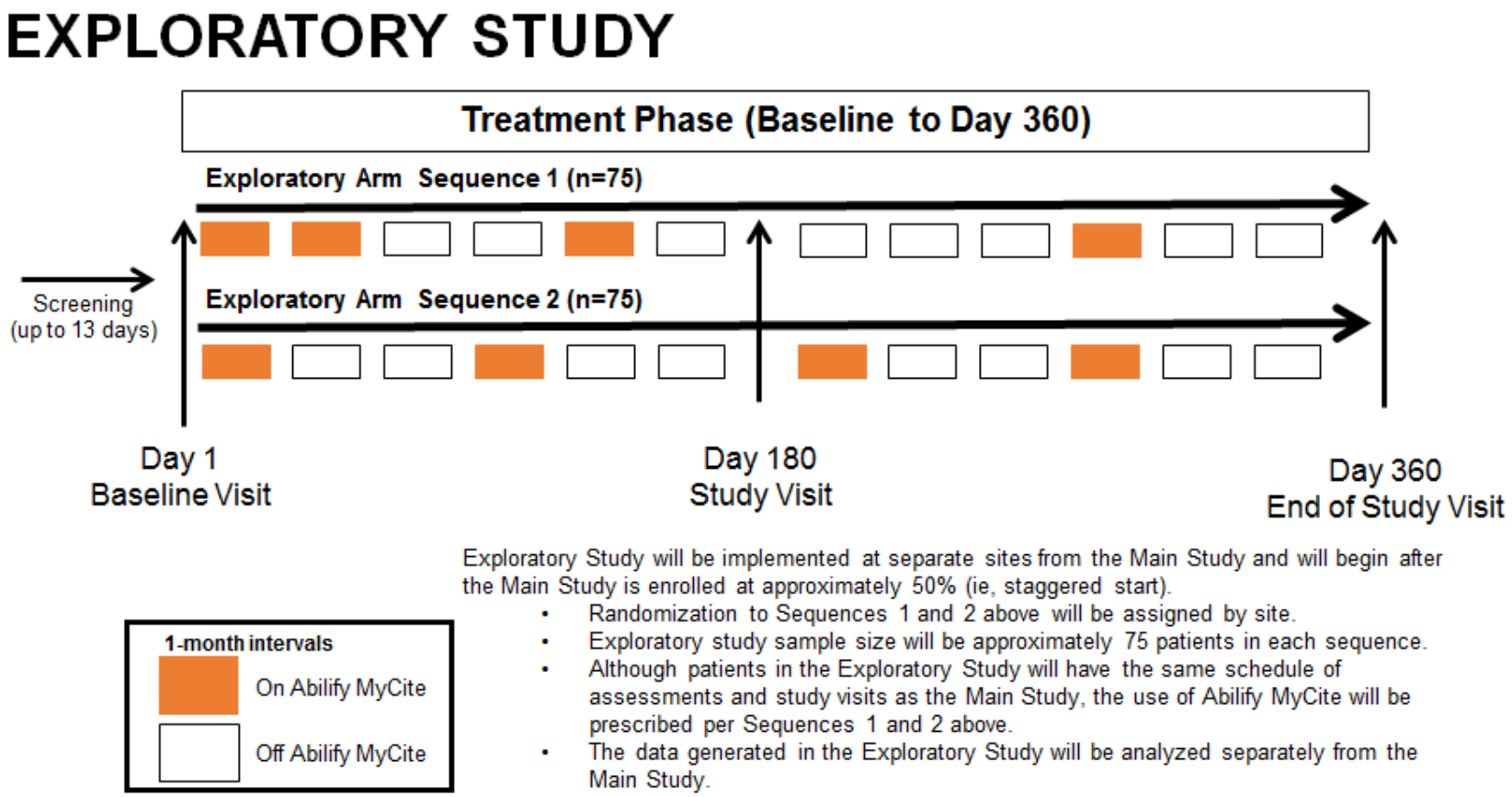


Figure 3.1-3 Study Design Schematic (Exploratory Study)

3.1.1 Main Study

The study design schematic for the main study in provided in Figure 3.1-2.

This is a phase 4, open-label, prospective, pragmatic clinical trial to assess the difference between all-cause hospitalizations in patients using Abilify MyCite (for Months 1-3, then prohibited for Months 4-6) versus virtual matched controls from baseline to Day 180. Virtual matched controls CCI would be receiving treatment as usual (ie, any product other than Abilify MyCite, which may be oral aripiprazole or any other product).

Eligible patients will enter a screening period of up to 13 days. For patients enrolling into the study, those not on aripiprazole at screening will use the screening period for conversion to aripiprazole from other antipsychotics according to the approved labels. At the baseline visit (which may be the same visit as the screening visit), Abilify MyCite onboarding will be provided in the office, with commercial informational materials and additional call center support; then, patients will initiate 3 months of treatment with Abilify MyCite at the baseline visit.

During the following 3 months (Months 4 through 6), use of Abilify MyCite will be prohibited (and the patient continues with oral aripiprazole or other appropriate treatment, per routine clinical care). The primary endpoint will be assessed at Day 180. The final study visit will be on Day 180 for patients not continuing in the second, optional interventional period.

After the visit at Day 180, a second, optional interventional period (up to 6 months of Abilify MyCite) may be initiated per the joint decision of the patients with their study physician; patients in this second, optional interventional period will have a visit at Day 360 (in addition to their regular visits as clinically indicated). During this second, optional interventional period, patients may start and stop Abilify MyCite as clinically indicated.

Enrolled patients will be matched to a virtual control group identified from CCI in a 1:3 ratio (enrolled patients on Abilify MyCite treatment versus virtual matched controls).

CCI the matching will be performed after the Abilify MyCite arm has been completed.

3.1.2 Exploratory Study

The study design schematic for the parallel exploratory study in provided in Figure 3.1-3. The parallel exploratory study will utilize a different set of physicians and patients from the main study. Results from the exploratory study will be analyzed separately from the main study results.

Procedures for the exploratory study will be similar to those in the main study (see Section 3.1.1), with the exception that there will be 1-month intervals of Abilify MyCite use (and 1-month intervals of prohibition of Abilify MyCite use), as diagrammed in the study schematic (Figure 3.1-3). During periods of nonuse of Abilify MyCite, the patient continues with oral aripiprazole, per routine clinical care.

In the exploratory study, each patient will receive Abilify MyCite per 1 one of 2 sequences over a 360-day period:

- Sequence 1: Only in Months 1, 2, 5, and 10.
- Sequence 2: Only in Months 1, 4, 7, and 10.

Sites will be randomized to 1 of the 2 sequences.

For this exploratory study, the site visits will be at screening, baseline (which may be the same day as the screening visit), Day 180, and Day 360; additional visits are to occur as clinically indicated. The exploratory arm will begin after the main study is enrolled at approximately 50% (ie, staggered start).

3.2 Study Population

Enrollment is described in Section 3.2.1 (main study) and Section 3.2.2 (exploratory study).

For information on the virtual matched control group, see Section 3.5.4.

3.2.1 Main Study

The main study will enroll approximately 640 adult patients with SCH, BP1, or MDD who, within 60 days prior to study enrollment, had a hospitalization (all-cause or psychiatric, ie, for any reason) or at least 1 psychiatric partial hospital admission. To achieve balanced enrollment of the targeted diagnoses, a minimum enrollment of each diagnosis will be 25% or approximately 160 total patients.

3.2.2 Exploratory Study

The exploratory study will utilize different physicians and patients from the main study.

The exploratory study will enroll approximately 150 adult patients (75 per sequence) with SCH, BP1, or MDD who, within 60 days prior to study enrollment, had a hospitalization (all-cause or psychiatric) or at least 1 psychiatric partial hospital admission.

As with the main study, to achieve balanced enrollment of the targeted diagnoses, a minimum enrollment of each diagnosis will be 25%, or approximately 37 patients. The exploratory arm will begin after the main study is enrolled at approximately 50% (ie, staggered start).

3.3 Eligibility Criteria for Physicians and Patients (Main and Exploratory Studies)

All of Section 3.3 applies to both the main study and the exploratory study. The procedures refer to physicians and patients at the study sites; for information on the virtual matched control group, see Section 3.5.4.

3.3.1 Informed Consent

An informed consent form (ICF) fully describing the purpose, procedures, and potential risks and benefits of the study will be developed and approved by the Institutional Review Board / Independent Ethics Committee (IRB/IEC) prior to study initiation. The study physician must ensure that each study patient is fully informed of the study and authorizes release of health information prior to study enrollment. Written informed consent will be obtained prior to initiation of any study-related procedures. The patient will receive a copy of the signed ICF. The study physician will retain the original signed ICF for each patient. The IRB/IEC must prospectively approve the ICF and any changes to the ICF during the course of the study before use.

3.3.2 Physician Practice Eligibility

Enrollment of approximately 100 physician sites overall (ie, main study plus exploratory study) from the Anthem Network of providers in the United States (US) is planned for this study. HealthCore will identify potential physicians for the study by analyzing CCI [redacted] to identify physicians who provide care for a high volume of patients who potentially meet basic inclusion criteria sufficient to support study enrollment goals.

Physicians (and patients) in the main study will be distinct from those in the exploratory study.

3.3.3 Patient Recruitment and Eligibility

Patients will be recruited for enrollment when they interact with their physician as part of their standard of care. Eligible participants include adult patients with a current diagnosis of SCH, BP1, or MDD being treated with aripiprazole, or for whom aripiprazole treatment would be appropriate, as determined by the treating physician. Patients must also meet all of the inclusion criteria (Section 3.3.4) and none of the exclusion criteria (Section 3.3.5).

3.3.4 Patient Inclusion Criteria

For enrollment into the study, patients are required to meet the following inclusion criteria:

Table 3.3.4-1	**Inclusion Criteria**
1.	Patients are actively enrolled in an Anthem-affiliated commercial, Medicaid, or Medicare health plan with medical and pharmacy benefits.
2.	Male and female patients between the ages of 18 and 63 years, inclusive at the time of consent.
3.	Patients must have a smartphone with data plan.
4.	Patients must have a current diagnosis of SCH, BP1, or MDD.
5.	Patients currently prescribed aripiprazole, or appropriate for aripiprazole treatment.
6.	Within 60 days prior to study enrollment, patients are required to have had a hospitalization (all cause or psychiatric) or at least 1 psychiatric partial hospital admission.
7.	Patients are deemed appropriate, per the study physician judgment, to use Abilify MyCite per the package insert and to enter this interventional study.
8.	Patients must be able to read and understand English.

3.3.5 Patient Exclusion Criteria

For enrollment into the study, patients will be excluded if they fall under any of the following exclusion criteria.

Table 3.3.5-1	**Exclusion Criteria**
1.	Any patient who participated in another clinical trial within 30 days of enrollment into the current study.
2.	Females who are breast-feeding and/or who are pregnant at the time of study enrollment, or who plan to become pregnant during the study.
3.	Patients who are currently being treated with a long-acting injectable antipsychotic.

3.4 Outcome Variables

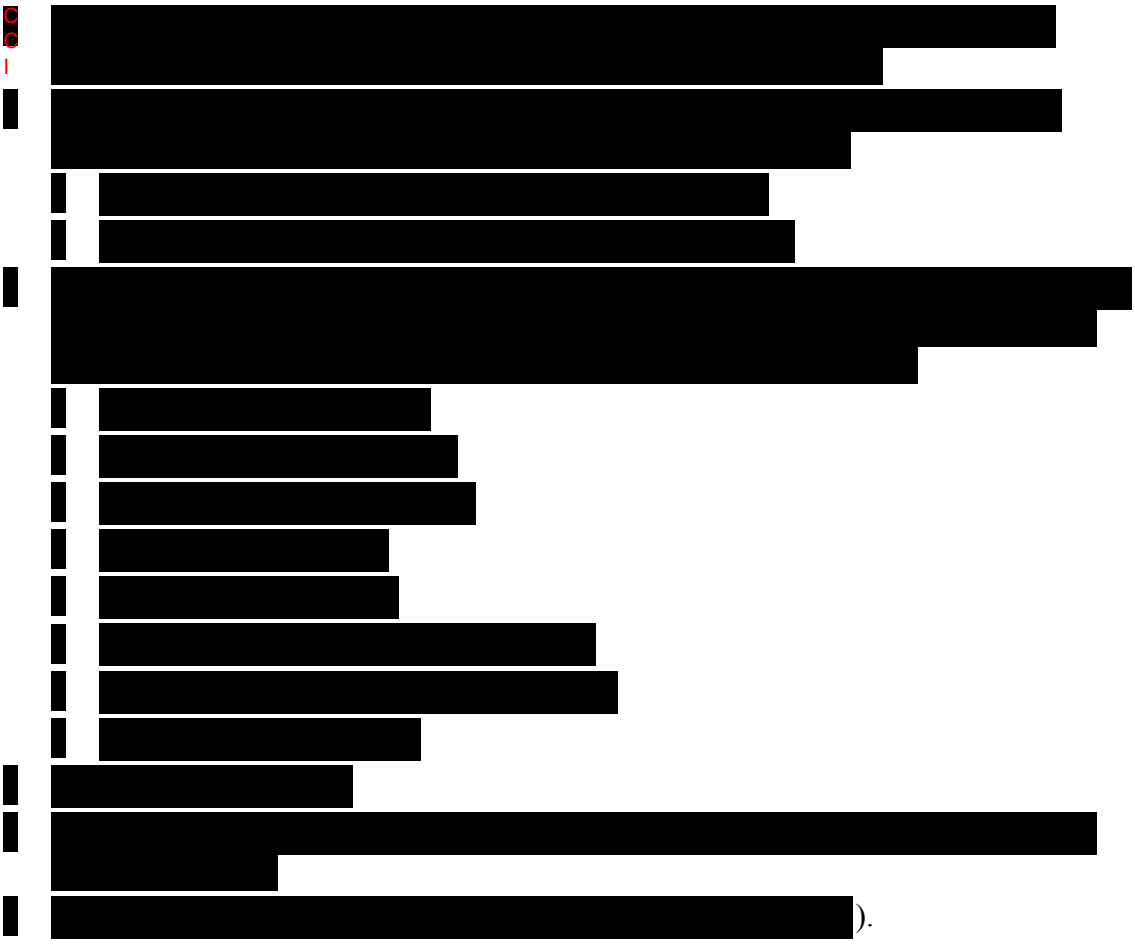
3.4.1 Primary Endpoint (Main Study)

The primary endpoint is the difference in the proportion of patients with all-cause hospitalizations for patients using Abilify MyCite versus virtual matched controls from baseline to Day 180.

3.4.2 Secondary Endpoints (Main Study)

The secondary endpoint is the difference between groups (Abilify MyCite versus virtual matched controls) in the proportion of patients with at least 80% proportion of days covered (PDC) (with antipsychotic medication) from baseline to Day 180.

3.4.3 Exploratory Endpoints (Main Study)



).

CCI

3.4.4 Endpoints for the Exploratory Study

For the exploratory study, as applicable, endpoints described in Section 3.4.1, Section 3.4.2, and Section 3.4.3 will be assessed for Sequence 1 vs Sequence 2 as a post-hoc analysis. Results from the exploratory study will be analyzed separately from the main study results.

3.5 Study Procedures

3.5.1 Main Study: Schedule of Assessments

Study assessment time points for enrolled patients are summarized for the main study in Table 3.5.1-1.

Procedures for enrolling patients into the study are described in Section 3.5.1.2.

CCI

CCI [redacted]

Table 3.5.1-1	**Main Study: Schedule of Assessments (for Patients Enrolled at Sites)**								
	Screening[a]	**Interventional Phase**[b]				**Mid-study (or End-of-study) Visit**[c,d]	**Optional 2nd Abilify MyCite Treatment**[d]	**End-of-study Visit**[e]	CCI [redacted]
	≤13 days[a]	**Baseline (Day 1)**[a]	**Day 30±7**	**Day 60±7**	**Day 90±7**	**Day 180±7**	**Days 180-≤360**	**Day ≤360±7**	**Days 1- 360**
Study site visit	X	X				X		X[e]	
Informed consent	X								
Inclusion/exclusion criteria assessment	X								
Smartphone and data plan verification	X								
Demographic information and medical / psychiatric history		X							
Height and weight measured		X							
Vital signs		X							
Onsite onboarding with Abilify MyCite; patient pairs and applies patch		X							
Dispense patches, aripiprazole + IEM, and other supplies		X					X		
Physician reviews Abilify MyCite dashboard data every 2 weeks[f]			-----x[f]----	-----x[f]----	-----x[f]----	----------x[f]---------	--------x[f]-------	-----x[f]---	

Table 3.5.1-1 Main Study: Schedule of Assessments (for Patients Enrolled at Sites)

	Screening[a]	Interventional Phase[b]				Mid-study (or End-of-study) Visit[c,d]	Optional 2nd Abilify MyCite Treatment[d]	End-of-study Visit[e]	CCI
	≤13 days[a]	Baseline (Day 1)[a]	Day 30±7	Day 60±7	Day 90±7	Day 180±7	Days 180-≤360	Day ≤360±7	Days 1- 360
CCI									
Concomitant medications									X[h]
Hospitalizations (all-cause and psychiatric)									X[h]
CCI									

[a]The screening and baseline visits can be combined.

[b]The interventional period begins with the baseline visit and ends at the Day 180 visit (or early termination [ET] if the patient withdraws or is withdrawn from the study prematurely). Clinical data will be collected as part of routine clinical practice, not as a requirement for the protocol.

[c]All patients will complete the Day 180 visit. If a patient withdraws or is withdrawn from the study prematurely (eg, before completing the scheduled Day 180 visit), then an early ET visit should be performed, at which time all assessments and procedures that were to have been performed at the Day 180 visit should be completed. In such cases, the reason for the ET must be recorded.

[d]At the Day 180 visit, a second, optional interventional period (up to 6 months of Abilify MyCite; Days 180-≤360) may be initiated per the joint decision of the patients with their study physician. If the patient is not continuing in the optional second Abilify MyCite treatment period (Days 180-≤360), then the Day 180 visit is the final visit. Patients need to be on aripiprazole to use the system for the optional second treatment period.

[e]The Day 360 visit (and activities) are only completed for patients in the optional second Abilify MyCite treatment period (Days 180-≤360). If a patient withdraws or is withdrawn from the study prematurely (eg, before completing the scheduled Day 360 visit), then an early ET visit should be performed, at which time all assessments and procedures that were to have been performed at the Day 360 visit should be completed. In such cases, the reason for the ET must be recorded.

[f]The study 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]If a patient does not have a routine care visit at Day 30, Day 60, or Day 90, the scale will be administered by phone.

[h]Data collected if available per routine clinical practice CCI [redacted] at completion of the study (plus 3 months to allow for lag in CCI [redacted] patient data from baseline through end of study will be included. CCI [redacted]

3.5.1.1 CCI

[redacted]

Data will also be collected from a virtual matched control group, as described in Section 3.5.4.

3.5.1.2 Main Study: Enrollment Procedures

The study physician will make the decision regarding the patient's suitability for the study. The determination that a patient is appropriate for treatment with aripiprazole (regardless of whether or not they would switch from current treatment) and initiation of Abilify MyCite will be made prior to and independent of study initiation. Following the treating physician's determination of eligibility, patients will be approached for enrollment. As part of their routine office visits, patients will be approached for potential enrollment into the study by their treating physician.

3.5.1.3 Main Study: Screening

Eligibility assessment per the treating physician's decision and informed consent will be conducted during a screening visit up to 13 days prior to and including the baseline visit.

For patients enrolling into the study, those not on aripiprazole at screening will use the screening period for conversion to aripiprazole from other antipsychotics according to the approved labels.

3.5.1.4 Main Study: Baseline

The baseline visit marks the beginning of the interventional phase. Patients will receive training and onboarding with Abilify MyCite as outlined in Table 3.5.1-1. Training will be based on the commercial training materials for Abilify MyCite to reflect real-world practice. Baseline assessments will include: demographic data, medical and psychiatric history, height, weight, vital signs, and hospitalization history (all-cause and psychiatric). CCI [redacted]

3.5.1.5 Main Study: Treatments

Patients will initiate Abilify MyCite upon study enrollment (at the baseline visit) and will continue use through Day 90 (with an optional second use period over Days 180-≤360),

as deemed clinically appropriate by their treating physician. Abilify MyCite may be started and stopped as clinically appropriate based on physician judgment. Ability MyCite metrics will be captured throughout use.

During periods of nonuse of Abilify MyCite, the patient continues with oral aripiprazole or other appropriate treatment, per routine clinical care.

3.5.1.6 Main Study: Interventional Phase (Day 1 to Day 180)

After the baseline visit, there are no mandated visits until Day 180. However, it is anticipated that patients will undergo medical evaluation at regular intervals. Data collected at these routine care visits, such as Abilify MyCite use changes and AEs (as described in Section 4), will be entered into the study database. Physicians are expected to regularly review the Abilify MyCite dashboard data during active Abilify MyCite use as consistent with routine care, approximately every 2 weeks.

At the time points indicated in Table 3.5.1-1, the patient, caregiver (if applicable), and physician outcomes scales will be completed.

3.5.1.7 Main Study: Day 180 Mid-study (or End-of-study) Visit

The Day 180 visit marks the end of the interventional phase. All patients will complete the Day 180 visit. Data collected at the Day 180 visit, such as Abilify MyCite use changes and certain AEs (as described in Section 4), will be entered into the study database. CCI [redacted]

At the Day 180 visit, a second, optional interventional period (up to 6 months of Abilify MyCite; Days 180-≤360) may be initiated per the joint decision of the patients with their study physician; if the patient is not continuing into the optional period, then the Day 180 visit is the final visit. During this second, optional interventional period, patients may start and stop Abilify MyCite as clinically indicated.

If a patient withdraws or is withdrawn from the study prematurely (eg, before completing the scheduled Day 180 visit), then an early ET visit should be performed, at which time all assessments and procedures that were to have been performed at the Day 180 visit should be completed. In such cases, the reason for the ET must be recorded.

3.5.1.8 Main Study: Second Interventional Period (Day 180 to Day 360)

At the Day 180 visit (or later during the Day 180-<360 period), patients will decide jointly with their study physician whether to restart Abilify MyCite for a second interventional period (Days 180-≤360). Patients will re-initiate Abilify MyCite at Day 180 (or later during the Day 180-<360 period) and the second interventional period

will proceed similarly to the interventional period described in Section 3.5.1.6. Data collected at routine care visits between Day 180 and Day 360, such as Abilify MyCite use changes and AEs (as described in Section 4), will be entered into the study database. Physicians are 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 patients need to be on aripiprazole to use the system for the optional second treatment period.

CCI [redacted]

If a patient withdraws or is withdrawn from the study prematurely (eg, before completing the scheduled Day 360 visit), then an early ET visit should be performed, at which time all assessments and procedures that were to have been performed at the Day 360 visit should be completed. In such cases, the reason for the ET must be recorded.

3.5.1.9 CCI [redacted]

[redacted]

Additional patient data will be collected if available per routine clinical practice, eg, prior (up to 12 months) hospitalizations (all-cause and psychiatric) and concomitant medications.

3.5.2 Exploratory Study: Schedule of Assessments

Study assessment time points for enrolled patients are summarized for the exploratory study in Table 3.5.2-1.

Procedures for the exploratory study will be similar to those in the main study (Section 3.5.1.1 through Section 3.5.1.5, and Section 3.5.1.9), with the exception that there will be 1-month intervals of Abilify MyCite use (and 1-month intervals of prohibition of Abilify MyCite use), as diagrammed in the study schematic (Figure 3.1-3). During periods of nonuse of Abilify MyCite, the patient continues with oral aripiprazole, per routine clinical care. If the patient goes on another (non-aripiprazole) treatment, data will be collected, but the patient will not return to Abilify MyCite if that treatment is not appropriate.

For the exploratory study, the site visits will be at screening, baseline (which may be the same day as the screening visit), Day 180, and Day 360; additional visits are to occur as clinically indicated, and assessments will occur at the times indicated in Table 3.5.2-1.

Table 3.5.2-1 Exploratory Study: Schedule of Assessments (for Patients Enrolled at Sites)

	Screening[a]	Interventional Phase[b]					End-of-study Visit[c]	CCI [redacted]
	≤13 days[a]	Baseline (Day 1)[a]	Day 30±7	Day 60±7	Day 180±7	Day 300±7	Day 360±7	Days 1- 360
Study site visit	X	X			X		X	
Informed consent	X							
Inclusion/exclusion criteria assessment	X							
Smartphone and data plan verification	X							
Demographic information and medical / psychiatric history		X						
Height and weight measured		X						
Vital signs		X						
Onsite onboarding with Abilify MyCite; patient pairs and applies patch		X						
Dispense patches, aripiprazole + IEM, and other supplies[d]		X	-----x----	-----x----	-----x----	-----x----	-----x----	
Physician reviews Abilify MyCite dashboard data every 2 weeks[e]			-----x----	-----x----	-----x----	-----x----	-----x----	
CCI [redacted]			[redacted]	[redacted]		[redacted]		
[redacted]			[redacted]	[redacted]		[redacted]		
[redacted]			[redacted]	[redacted]		[redacted]		
[redacted]		[redacted]			[redacted]		[redacted]	
[redacted]		[redacted]			[redacted]		[redacted]	

Table 3.5.2-1 Exploratory Study: Schedule of Assessments (for Patients Enrolled at Sites)

	Screening[a]	Interventional Phase[b]					End-of-study Visit[c]	CCI [redacted]
	≤13 days[a]	Baseline (Day 1)[a]	Day 30±7	Day 60±7	Day 180±7	Day 300±7	Day 360±7	Days 1- 360
Concomitant medications								X[g]
Hospitalizations (all-cause and psychiatric)								X[g]
CCI [redacted]								[redacted]

Seq = Sequence.

[a]The screening and baseline visits can be combined.

[b]The interventional period begins with the baseline visit and ends at the Day 360 visit (or ET if the patient withdraws or is withdrawn from the study prematurely). Clinical data will be collected as part of routine clinical practice, not as a requirement for the protocol.

[c]All patients will complete the Day 360 visit. If a patient withdraws or is withdrawn from the study prematurely (eg, before completing the scheduled Day 360 visit), then an early ET visit should be performed, at which time all assessments and procedures that were to have been performed at the Day 360 visit should be completed. In such cases, the reason for the ET must be recorded.

[d]The physician will dispense Abilify MyCite supplies (patches, aripiprazole + IEM, and other supplies) during routine visits as required during the study per Sequences 1 and 2. Note that "----x----" indicates the activity can occur multiple times during the period.

[e]The study 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 that the activity will occur multiple times during the period.

[f]If a patient does not have a routine care visit at the given visit, the scale will be administered by phone.

[g]Data collected will be collected CCI [redacted] at completion of the study (plus 3 months to allow for lag in CCI [redacted] patient data from baseline through end of study will be included. CCI [redacted]

3.5.3 Assessments (Main and Exploratory Studies)

3.5.3.1 Adverse Events

Refer to Section 4 (Reporting of Adverse Events).

CCI

CCI

[redacted]

3.5.4 Virtual Matched Control Group (Main Study Only)

CCI

[redacted]

The virtual matched control group is not applicable for the exploratory study.

3.5.5 End of Study

The End of Study Date is defined as the last Date of Contact or the Date of Final Contact Attempt for the last patient completing or withdrawing from the study, plus a 3-month lag time to allow for CCI [redacted]

The End of Study Date will be the last date overall (main study or exploratory study).

3.6 Stopping Rules, Withdrawal Criteria, and Procedures

3.6.1 Entire Study

Otsuka and/or the IRB/IEC reserve the right to terminate the study at any time. In this event, all data collection will end. After the collected data is received, study physicians will be compensated as contractually agreed. If Otsuka terminates or suspends the study for safety or unanticipated other reasons, prompt notification will be given to study sites, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

3.6.2 Individual Site

The IRB/IEC reserves the right to terminate participation of individual study sites at any time. Individual study sites may also be terminated for cause by Otsuka per contractual agreement. In such cases, all data collection at terminated study sites will end. After the collected data is received, the study physicians will be compensated as contractually agreed.

The sponsor should be notified promptly if the study is terminated by the physician or the IBR/EC at the site.

3.6.3 Individual Patient

Patient withdrawal from the study will be based upon physician clinical determination and/or patient decision. Participation in the study is voluntary, and all patients are free to terminate their participation at any time. In the event of study withdrawal, the study physician will record the reason for study withdrawal and continue to follow-up with the patient for any unresolved SAEs. Upon patient withdrawal from the study, all data collection will end, but all study data collected up to withdrawal will be included in the study database.

In addition, patients falling under the following criteria must be withdrawn from the study:

- occurrence of any intercurrent illness or abnormality in a laboratory assessment which, in the opinion of the physician, warrants the patient's permanent withdrawal from the study;
- at the request of the patient or physician;
- patient becomes pregnant; or
- patient is lost to follow-up.

3.6.4 CCI [redacted]

[redacted]

3.7 Protocol Deviations

As this is a real-world study, the chances of protocol deviations occurring in this study are minimal and limited to data breaches, deviations to Good Clinical Practice, or treatment outside of the parameters of the Abilify MyCite US package insert.

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process or patient enrolled in violation of eligibility criteria), the study physician will notify HealthCore, who will contact the sponsor at the earliest possible time by telephone. The study physician and sponsor will come as quickly as possible to a joint decision regarding the patient's continuation in the study. This decision will be documented by the study physician and the sponsor.

4 Reporting of Adverse Events

In this phase 4 study, all SAEs (ie, drug-related SAEs and device-related SAEs), device-related nonserious AEs (ie, related to the device component of Abilify MyCite treatment, including those leading to withdrawal from Abilify MyCite), potential hepatotoxicity cases, and pregnancies will be monitored and collected. For device-related AEs leading to withdrawal from Abilify MyCite, the reason for withdrawal will be collected.

4.1 Definitions

4.1.1 Drug-related Serious Adverse Events

A serious adverse event (SAE) includes any event that results in any of the following outcomes:

- Death
- Life-threatening; eg, the patient was, in the opinion of the HCP, 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.
- 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 (eg, 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 patient 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.

4.1.2 Device-related Serious Adverse Events

A device-related SAE is defined as:

- 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:
  - 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 study, device-related SAEs include any event that is related to the IEM, patch, or the phone and application (reported to Otsuka).

4.1.3 Nonserious Adverse Events

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE (Section 4.1.1 and Section 4.1.2). As described above, only nonserious AEs that are related to the device (ie, related to the device component of Abilify MyCite, including those leading to withdrawal from Abilify MyCite) will be collected in this study.

4.1.4 Immediately Reportable Event

Immediately reportable events (IREs) include the events discussed in Section 4.1.1, Section 4.1.2, and any of the following outcomes:

- Any SAEs;
- Any AEs related to occupational exposure;
- Any device-related nonserious AEs, including skin irritation that is Grade 2 or worse (see Appendix 9), ie, definite erythema that is readily visible; minimal (or worse) edema or minimal (or worse) papular response;
- Potential drug-induced liver injury (DILI) case (see Section 4.4);
- 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 as an AE in the data collection tool, if there is an abnormality or complication;

If a patch-related nonserious AE occurs, the skin irritation scale should be completed; Grade 2 or above on the scale are considered medically significant for purposes of reporting.

4.1.5 Abnormal Clinical Laboratory Test Changes

Clinical laboratory assessments will be conducted at the HCPs' discretion to ensure safety of the patient. Ongoing clinical laboratory assessments are not required for this study.

In the event that the HCP orders a laboratory test in the interest of patient safety, it is the HCP's responsibility to review the results of all laboratory tests as they become available.

Abnormal laboratory tests that a physician deems related to the product would be considered a SAE and/or IRE if they fit the criteria set forth in Section 4.1.1, Section 4.1.2, and Section 4.1.4.

4.1.6 Severity

Adverse events will be graded on a 3-point scale and reported as indicated in the data collection tool. 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.

4.1.7 Abilify MyCite Causality

Assessment of causal relationship of an SAE or device-related nonserious 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 SAE or device-related nonserious AE.

Not Related: There is no temporal or causal relationship between Abilify MyCite and the SAE or device-related nonserious AE.

4.2 Eliciting and Reporting Serious Adverse Events

The HCP will assess patients for the occurrence of SAEs. To avoid bias in eliciting SAEs, patients should be asked the non-leading question: "How have you felt since your last visit?" All SAEs reported by the patient must be recorded on the source documents and data collection tool provided by the sponsor. Serious AE collection is to begin after a patient has signed the ICF. All SAEs will be collected starting from the signing of the ICF until the end of the study.

Use medical terminology in SAE reporting. Serious 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 SAE 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. An SAE that undergoes a change in severity, seriousness, or toxicity should be reported as a new SAE.

In addition, Clinical Safety and Pharmacovigilance must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 4.3. Special attention should be paid to recording hospitalization and concomitant medications.

4.3 Immediately Reportable Events

The HCP must immediately report after becoming aware of any SAE, potential DILI, confirmed pregnancy, or any device-related nonserious AEs (which include skin irritation that is Grade 2 or worse per Appendix 9, ie, definite erythema that is readily visible; minimal [or worse] edema or minimal [or worse] papular response) by telephone, fax, or e-mail to Clinical Safety and Pharmacovigilance using the contact information on the cover page of this protocol (see also Appendix 2). An IRE form must be completed and sent by e-mail, fax, or overnight courier to Clinical Safety and Pharmacovigilance.

Patients 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 HCP will provide or arrange appropriate supportive care for the patient and will provide prompt updates on the patient's status to Clinical Safety and Pharmacovigilance.

4.4 Potential Drug-induced Liver Injury

For a patient who receives laboratory tests, if the test indicates an elevation in aspartate aminotransferase or alanine aminotransferase 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, an IRE form for be completed, with all values listed.

4.5 Pregnancy

Females of childbearing potential (FOCBP) are defined as female patients or female partners of the male patients for whom menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).

Before study enrollment, FOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The patient must sign an ICF stating that the risks and consequences were discussed with her.

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

If a female patient is suspected to be pregnant before the patient receives Abilify MyCite, the investigator can recommend the patient undergo a pregnancy test with their general practitioner or primary care physician. If the pregnancy is confirmed, the patient must not receive Abilify MyCite and must not be enrolled in the study. If pregnancy is suspected while the patient is taking Abilify MyCite, Abilify MyCite may be continued at HCP discretion until the result of the pregnancy test is known. If pregnancy is confirmed, Abilify MyCite may be continued at HCP discretion based on treatment guidelines for the medication administered. If the HCP discontinues the patient from Abilify MyCite, it must be performed in an appropriate manner (eg, dose tapering if necessary for patient safety) and the patient will be withdrawn from the study. (Exceptions to study 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 HCP must immediately notify the sponsor of any pregnancy associated with Abilify MyCite exposure during the study and for 30 days for a female patient, 90 days for female partner of a male patient, after the last dose of Abilify MyCite, and record the event on the IRE form and forward it to the sponsor. Pregnancies of patients or their partners will be followed to term. In the event of pregnancy of a patient's partner, consent to follow the pregnancy will be obtained. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the HCP 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.

4.6 Follow-up of Serious Adverse Events

Serious AEs that are **identified or ongoing at the last scheduled contact** must be recorded in the data collection tool and reported to the Clinical Safety and Pharmacovigilance department according to the reporting procedures outlined in Section 4.3. This may include **unresolved previously reported SAEs, or new SAEs.** The HCP will follow SAEs until the events are resolved, stabilized, or the patient is lost to follow-up. Resolution means that the patient has returned to the baseline state of health and stabilized means that the HCP does not expect any further improvement or worsening of the patient's condition. The HCP will continue to report any significant follow-up information to Clinical Safety and Pharmacovigilance up to the point the event has been resolved.

4.6.1 Follow-up and Reporting of Serious Adverse Events Occurring after Last Scheduled Contact

Any new SAEs reported by the patient to the HCP that occur **after the last scheduled contact**, and are determined by the HCP to be reasonably associated with the use of Abilify MyCite, should be reported to Otsuka Pharmaceutical Development and Commercialization, Inc (OPDC).

This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined study period (eg, up to last scheduled contact). The HCP should follow SAEs identified after the last scheduled contact until the events are resolved, stabilized, or the patient is lost to follow-up. The HCP should continue to report any significant follow-up information to OPDC up to the point the event has been resolved or stabilized.

5 Data Collection

5.1 Data Sources

Data sources for this study include demographic and clinical data collected prospectively by study sites, data collected from Abilify MyCite, CCI [redacted]

CCI [redacted] In order to maintain patient confidentiality, each patient will be assigned a unique study-specific patient ID upon study enrollment to use in place of the patient name or any other identifying information (eg, medical record number). Data collected from Abilify MyCite will be transferred to HealthCore and integrated with prospectively collected study data, CCI [redacted] will be leveraged for analysis.

For data through the electronic case report forms (eCRFs), the study physician has the ultimate responsibility for the collection and reporting of all clinical and patient data and ensuring that the data are accurate and complete.

5.2 Electronic Case Report Forms and Electronic Data Collection

All clinical study data will be collected at the physician office or over the phone and entered into eCRF by trained site study personnel through a fully validated, 21 Code of Federal Regulations 11 and Health Insurance Portability and Accountability Act (HIPAA)-compliant EDC system.

All study personnel involved in data entry will be trained on patient confidentiality and the EDC system prior to beginning data entry. Site users will be provided eCRF Completion Guidelines to assist with study data collection and entry. Study personnel will access the EDC system through a secure study website.

6 Quality Control and Quality Assurance

6.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this study in an orderly manner in accordance with pragmatic research principles, applicable regulatory requirements, and local laws.

6.2 Auditing/Inspections

This study may be subject to audits or evaluations by regulatory authorities or Otsuka (or its designee). To enable such evaluations and/or audits, the study physician must agree to maintain and allow reasonable access to required patient and study records. The study physician agrees to keep the identity of all participating patients (sufficient information to link records, eg, hospital records), all original signed ICFs, SAE Forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls, reports).

Regulatory requirements for the archival of records for this study necessitate that participating physicians maintain detailed clinical data for a period of 3 years after the end of this study.

7 Statistical Methods and Planned Analyses

Complete details of the planned statistical analysis will be presented in the statistical analysis plan (SAP).

7.1 Sample Size

The primary endpoint for the study is the proportion of patients with at least 1 all-cause hospitalization from study start date to Day 180. The assumptions for the sample size calculation were based on input from CCI [redacted] for patients diagnosed with SCH, BP1, or MDD who had at least 1 all-cause hospitalization or partial psychiatric hospitalization within the 60 days prior to enrollment. A control group event rate of 36.3% was estimated, weighted based on an expected study distribution of 25% patients with SCH, 25% with BP1, and 50% with MDD. Sample size calculations were based on testing 2 proportions using the Z-test with unpooled variance. The study sample size of 447 patients was calculated based on the following assumptions, informed from CCI [redacted] 20% reduction in the proportion of patients with all-cause hospitalizations in the Abilify MyCite group versus the virtual matched control group (29.04% Abilify MyCite versus 36.30% virtual matched control), 1:3 (Abilify MyCite : virtual matched controls) matching, 80% power, and maintaining an overall alpha level of 0.05 with the level of significance in a superiority hypothesis of 0.025. Sample size calculations will be documented in the SAP. Using a 30% dropout rate at 6 months, a sample size of 640 patients will need to be enrolled to ensure completion of 447 patients.

A virtual control group of approximately 1350 patients will be identified from the CCI [redacted] and matched to the final sample of Abilify MyCite patients. This will create 3 controls for every 1 Abilify MyCite patient, which reduces the required Abilify MyCite sample size as compared to a 1:1 match while maintaining statistical power. Controls will be matched to Abilify MyCite patients using a propensity score derived from CCI [redacted] This process has been shown to minimize bias associated with sample selection. Further details on the matching process will be included in the SAP.

7.2 Analysis of Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the study population overall and by treatment (Abilify MyCite versus virtual matched controls). Discrete

variables will be reported as count (frequency) and percent for each category. Continuous level variables (interval, ratio) will be reported as mean and standard deviation. Where applicable, range, minimum, maximum, and median will also be reported. Other statistics, measures of central tendency, and measures of dispersion may also be reported as outlined in the SAP.

It is likely that the virtual matched controls will lack some variables that are available to the Abilify MyCite sample. As a result, a comprehensive list of each variable in the Abilify MyCite sample will be listed, while "N/A" will be listed for each variable that is not available in the virtual matched control cohort. Balance in baseline characteristics across the 2 cohorts will be evaluated prior to analysis.

The details of this analysis will be fully described in the SAP.

7.3 Effectiveness Analyses

Effectiveness analysis for this study refers to the difference in the study endpoints within the Abilify MyCite cohort and the virtual matched controls. This analysis is further outlined in the primary endpoint and secondary endpoints sections (Section 7.3.1 and Section 7.3.2). A summary table will be presented reporting the difference between cohorts at Day 180. Potential adjustment for baseline values or differences that exist in the samples will be further outlined in the SAP.

7.3.1 Primary Endpoint

The primary endpoint compares the proportion of patients with all-cause hospitalizations between the Abilify MyCite and virtual matched control cohorts. The primary endpoint analysis will be a test of independent proportions. Standard methods for these analysis methods were developed by Fleiss and others[15] and included in all statistical software systems.

These tests are directional in nature since the alternative hypothesis is that the proportions in the Abilify MyCite cohort will be lower than the proportions in the virtual controls.

Adjustments will be made to the alpha level to account for the one-tail nature of the alternative hypothesis (HA).

- H_0: $P_1 - P_2 \geq 0$ versus H_A: $P_1 - P_2 < 0$

Where:

- P1 = proportion of Abilify MyCite patients with all-cause hospitalization from study start date to Day 180

- P2 = proportion of virtual control patients with all-cause hospitalization from study start date to Day 180

7.3.2 Secondary Endpoint

The secondary endpoint compares the difference between groups (Abilify MyCite versus virtual matched controls) in the proportion of patients with at least 80% PDC (with antipsychotic medication) from baseline to Day 180.

This analysis will be a test of independent proportions between the Abilify MyCite and virtual matched control groups.

7.3.3 Exploratory Endpoints

Details for the analysis of all exploratory endpoints (see Section 3.4.3 and Section 3.4.4) will be outlined in the SAP. It is understood that the list of variables might not be inclusive at this point and that alterations to these variables may be performed.

7.4 Safety Analyses

All safety summaries will be descriptive in nature. A detailed description of the summaries for the safety exploratory endpoint (see Section 3.4.3 [main study] and Section 3.4.4 [exploratory study]) will be described in the SAP.

7.5 Other Analyses

There are no plans to include any other analysis other than what has been described above. Any post-hoc testing that might arise from the results or findings will be discussed and conducted in accordance with standard and accepted statistical procedures.

7.6 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to progress notes, electronic data, and recorded data from automated instruments. In this pragmatic trial, source documents will reside in the patient's medical record. All source documents pertaining to this study will be maintained by the study physicians and made available for direct inspection by authorized persons. Study physicians will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF.

7.7 Data Collection

See Section 5 for study procedures relating to data collection.

7.8 File Management and Records Retention at the Study Site

In this pragmatic trial, the majority of study documents will be site medical records. Regulatory requirements for the archival of records for this study necessitate that participating physicians maintain detailed clinical data for a period of 3 years after the end of this study. The study physician will take measures to prevent accidental or premature destruction of these documents.

Record retention at the study site is also addressed in Section 6.2.

8 Ethics and Responsibility

All study activities will be conducted in accordance with regulatory guidelines for real-world, pragmatic research. Study personnel at physician sites will be provided training on the study protocol, the ICF, data collection, and data entry to ensure both the protection of potential study patients as well as the scientific integrity of the study. Sites will be monitored remotely, with onsite monitoring employed only for cause.

8.1 Institutional Review Board / Independent Ethics Committee

The study physician must obtain prospective approval of the study protocol, ICF, and any patient information or recruiting materials, if applicable, prior to commencement of any study activities. All changes in research activity and all unanticipated problems involving risk to human patients or others must be reported promptly to the IRB/IEC.

The study physician will obtain continued review of the study at intervals not to exceed one year or otherwise specified by the IRB/IEC.

9 Confidentiality

All information generated in this study will be considered highly confidential and will not be disclosed to anyone not directly concerned with the study without the sponsor's prior written permission. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All drugs, patient 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.

Patients will be identified only by initials and unique patient numbers in eCRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary.

9.1 Publication of Study Results

All information related to this study is considered confidential information belonging to Otsuka Pharmaceutical Development & Commercialization, Inc. and HealthCore as consistent with contractual agreement. A final study report will be generated following completion of data collection and analysis. Results and findings will be submitted to conferences and for publication in peer-reviewed scientific journals with authorship following the International Committee of Medical Journal Editors guidelines.

10 Amendment Policy

The study physician will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it be an overall change or a change for specific study site(s), must be handled as a protocol amendment written by the sponsor or its designee. In the case of a protocol amendment, the study physician must sign the revised protocol and the amendment will be submitted to the IRB/IEC and approval prior to implementation of any changes specified in the protocol amendment.

When the IRB/IEC, study physicians, and/or the sponsor conclude that the protocol amendment substantially alters the study design and/or increases the potential risk to the patient, the ICF must be revised and submitted to the IRB/IEC for review and approval prior to implementation. The revised ICF must then be used to obtain consent from new patients entering the study as well as from currently enrolled patients if they are affected by the amendment, per IRB/IEC guidance.

11 References

1 ABILIFY MYCITE (aripiprazole tablets with sensor) US Prescribing Information. Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan, Proteus Digital Health, Inc., Redwood City, CA, and Otsuka America Pharmaceutical, Inc, Rockville MD; 2017.

2 Rohatagi S, Profit D, Hatch A, Zhao C, Docherty JP, Peters-Strickland TS. Optimization of a Digital Medicine System in Psychiatry. J Clin Psychiatry. 2016;77(9):e1101-e1107.

3 PPD A formative usability study of the Otsuka MIND1 prototype by subjects with bipolar disorder or major depressive disorder. Otsuka Clinical Study Report for Protocol 316-13-204, issued 28 Jul 2014.

4 PPD A Multicenter, 8-week, Open-label, Single-arm, Exploratory Trial to Assess the Functionality of an Integrated Call Center for the Digital Medicine System by Adult Subjects With Schizophrenia (SCH), Major Depressive Disorder (MDD), or Bipolar 1 Disorder (BP1) Who Are Treated With Oral Aripiprazole. Otsuka Clinical Study Report for Protocol 316-13-215, issued 18 Nov 2016.

5 PPD Phase 1, open-label trial to evaluate the skin irritation potential and extent of adhesiveness of the RP4 patch following application to the skin of healthy, adult subjects. Otsuka Clinical Study Report for Protocol 316-13-205, issued 26 Feb 2014.

6 PPD A multicenter, 8-week, open-label study to assess usability of the Medical Information Device #1 (MIND1) System in adult subjects with schizophrenia who are treated with oral aripiprazole. Otsuka Interim Synopsis Clinical Study Report for Protocol 316-14-220, issued 27 Feb 2015.

7 Data on file. Abilify MyCite. Human factors engineering/usability engineering report: HCP/caregiver interface. NDA 207202. Otsuka Pharmaceutical Development & Commercialization, Inc. 2015b.

8 Peters-Strickland T, Pestreich L, Hatch A, Rohatagi S, Baker RA, Docherty JP, et al. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. Neuropsychiatr Dis Treat. 2016;12:2587-94.

9 Profit D, Rohatagi S, Zhao C, Hatch A, Docherty JP, Peters-Strickland TS. Developing a Digital Medicine System in Psychiatry: Ingestion Detection Rate and Latency Period. J Clin Psychiatry. 2016;77(9):e1095-e1100.

10 Kopelowicz A, Baker RA, Zhao C, Brewer C, Lawson E, Peters-Strickland T. A multicenter, open-label, pilot study evaluating the functionality of an integrated call center for a digital medicine system to optimize monitoring of adherence to oral aripiprazole in adult patients with serious mental illness. Neuropsychiatr Dis Treat. 2017;13:2641-51.

11 Peters-Strickland T, Hatch A, Adenwala A, Atkinson K, Bartfeld B. Human factors evaluation of a novel digital medicine system in psychiatry. Neuropsychiatric Disease and Treatment. 2018.

12 Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv. 1998;49:196-201.

13 Proteus Digital Health Wearable Sensor Investigator's Brochure Rev 7. Issued 22 Mar 2016.

14 Bloss CS, Wineinger NE, Peters M, Boeldt DL, Ariniello L, Kim JY, et al. A prospective randomized trial examining health care utilization in individuals using multiple smartphone-enabled biosensors. Peer J. 2016;4:e1554.

15 Fleiss JL. Statistical methods for rates and proportions. John Wiley & Sons; 1981.

Appendices

Appendix 1 Names of Sponsor Personnel

PPD

Phone: PPD
E-mail: PPD

PPD

Phone: PPD
E-mail: PPD

PPD

Phone: PPD
PPD

PPD HealthCore
PPD
Phone: PPD or PPD
E-mail: PPD

Appendix 2 Safety Reporting

For medical emergencies, the physician can contact the Global Safety and Pharmacovigilance department via a 24-hour telephone number: PPD A call to this telephone number does not alleviate the investigator's responsibility to report an SAE in writing, via fax.

Report Immediately Reportable Events (*SAEs, potential DILI, confirmed pregnancies, and any device-related nonserious AEs [eg, skin irritation that is Grade 2 or worse per Appendix 9]*) to the Global Safety and Pharmacovigilance department as follows:

Global Safety and Pharmacovigilance
Fax: PPD
E-mail: PPD

Appendix 3 Abilify MyCite Contents

Abilify MyCite Contents	
Abilify MyCite Component	**Description**
Aripiprazole + IEM	Aripiprazole tablet with sensor will be dispensed to the patients 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 patient for use. Each patch is designed for 7-day wear; extra devices are provided should the patients desire to change the patch more frequently during the period of familiarization or in case of sensor malfunction.
Computing Device & Accessories	Patients will use their own smartphone and required accessories. Patients 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 patient sleeps.
Abilify MyCite Reference Guide	A printed reference guide will provide explicit directions for normal use and troubleshooting.

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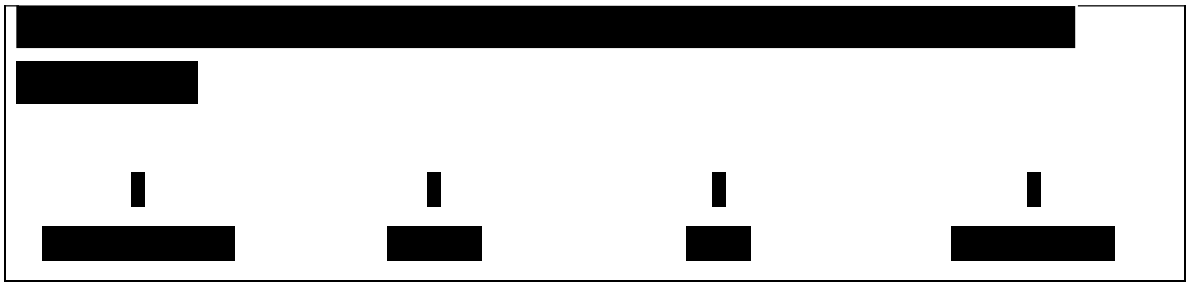

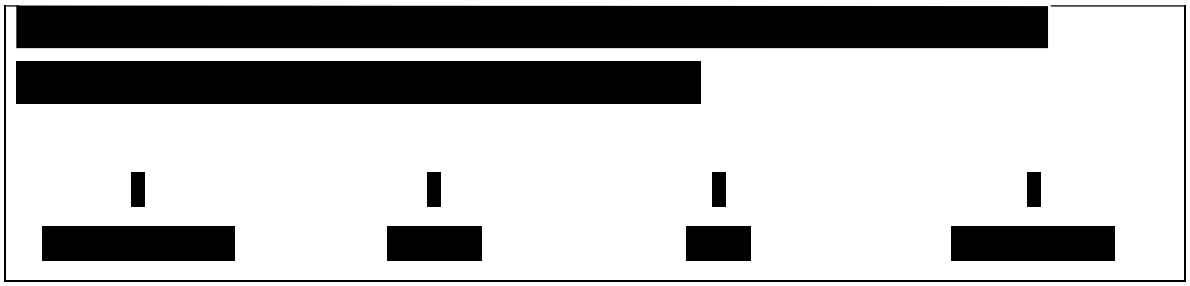

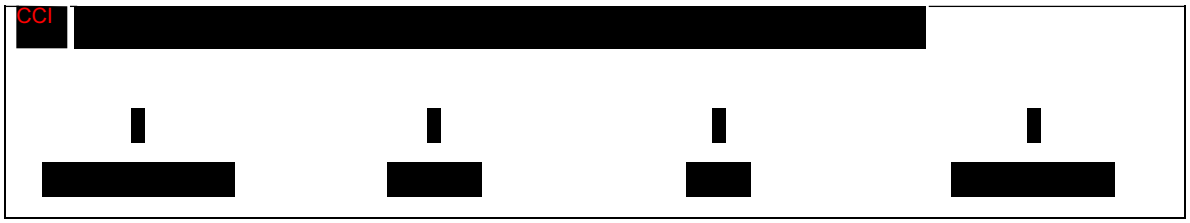
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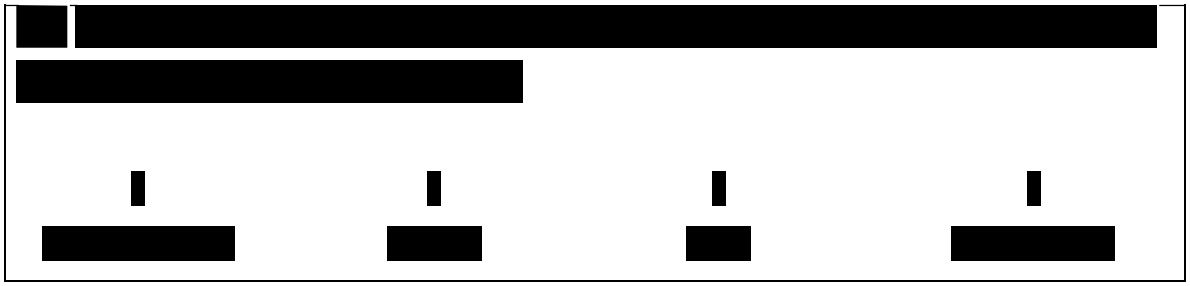

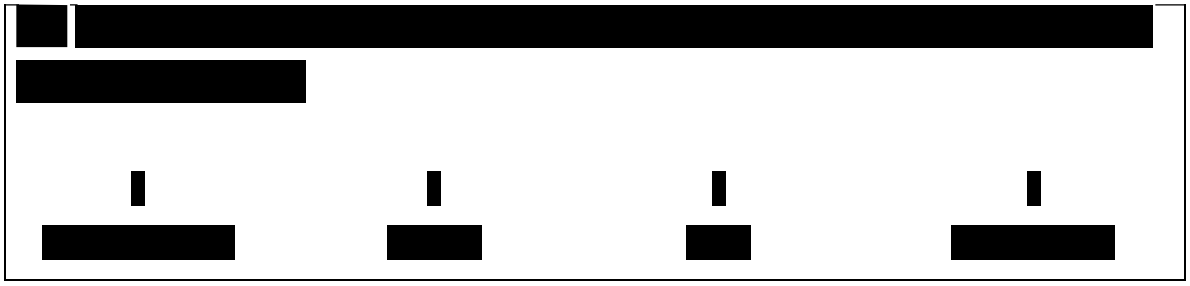

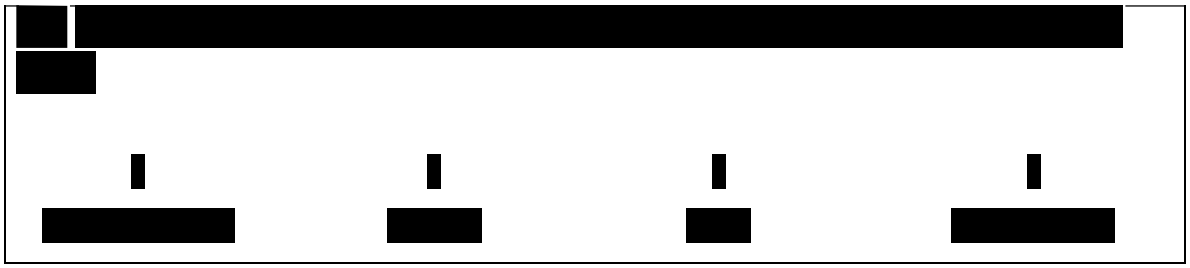

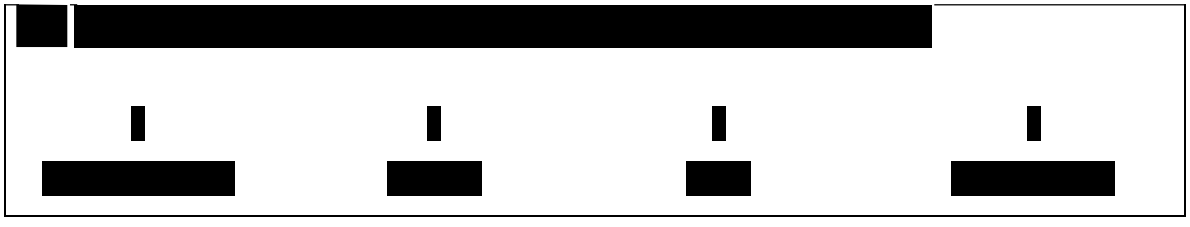

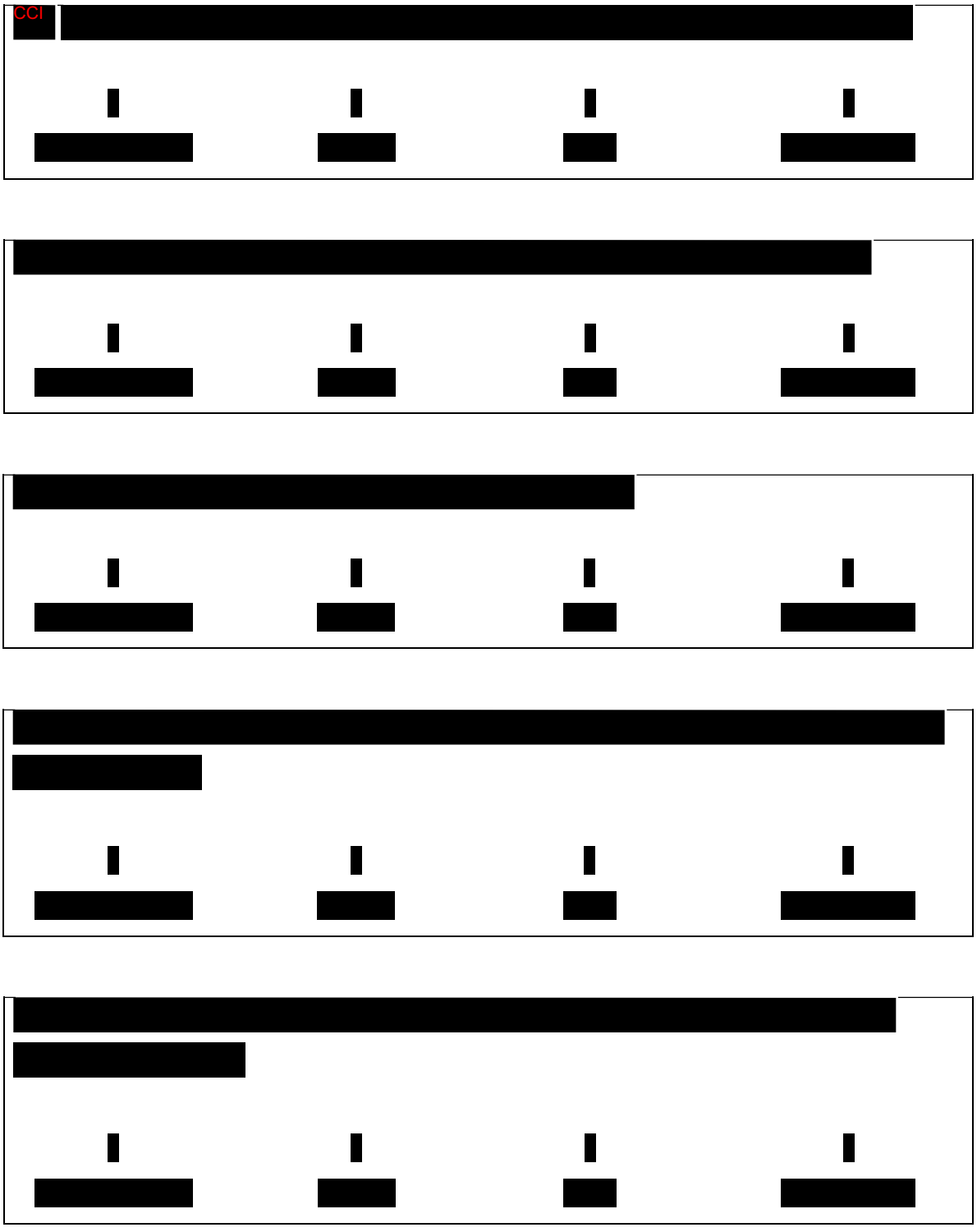
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Appendix 9 Skin Irritation Scoring System

Dermal Response:

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

Source: US Department of Health and Human Services, FDA Center for Drug Evaluation and Research, December 1999.

Investigator Agreement

I have read the protocol, *A Multicenter, 180-day Pragmatic Clinical Trial to Measure the Difference in All-cause Hospitalizations for Patients who are Using Abilify MyCite versus Virtual Matched Controls in Adults with Schizophrenia, Bipolar 1 Disorder, and Major Depressive Disorder* and agree to ensure that all staff members involved in the conduct of this study are informed of their obligations in meeting the commitments in accordance with it.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described pragmatic trial.

_____

Signature and Date

_____

Print Name

Otsuka Pharmaceutical Development & Commercialization, Inc.
This page is a manifestation of an electronically captured signature

MIND1

SIGNATURE PAGE

Document Name: 316-13-217 Protocol

Document Number: 0001286660

Document Version: 2.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Biostatistics Approval	08-Mar-2018 16:04 GMT+00
	Clinical Approval	08-Mar-2018 16:25 GMT+00