CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207202Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207202
Priority or Standard	Standard
Submit Date(s)	04/21/2017
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Division/Office	DPP/ODE1
Reviewer Name(s)	Daniel J. Lee, MD
Review Completion Date	10/26/2017
Established Name	aripiprazole
(Proposed) Trade Name	Abilify Mycite
Applicant	Otsuka Pharmaceutical Development and Commercialization, Inc
Formulation(s)	Oral tablet, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg
Dosing Regimen	once daily
Proposed Indication(s)	(b) (4)
Intended Population(s)	(b) (4)
Recommendation on Regulatory Action	Approve
Recommended Indication(s) (if applicable)	schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, bipolar I maintenance, and adjunctive treatment of major depression

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEALD	Study Endpoints and Labeling Development
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Aripiprazole is an atypical antipsychotic that received U.S. approval on November 15, 2002 (ABILIFY; NDA 021436). Aripiprazole is indicated for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, bipolar I disorder maintenance, adjunctive treatment of major depression, irritability associated with autistic disorder, and for the treatment of Tourette's disorder. Approved aripiprazole oral dosages range from 2mg to 30mg per day. Currently approved aripiprazole formulations include oral tablets, orally disintegrating tablets, oral solution, short-acting intermuscular injection, and a long-acting intramuscular injection.

The Applicant developed Abilify Mycite by embedding a sensor into aripiprazole tablets. The sensor powers on when exposed to stomach acid and transmits a signal to a wearable sensor (i.e., patch) placed over the upper left abdomen. The wearable sensor then transmits the data to a mobile application intended for patients and a web-portal intended for clinicians and caregivers. The Applicant developed Abilify Mycite (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant successfully demonstrated bioequivalence between approved oral aripiprazole tablets (the reference product) and oral aripiprazole tablets with embedded IEM in the original submission dated Jun 26, 2015. This application relies on FDA's previous efficacy and safety findings for the reference drug, aripiprazole oral tablets (NDA 021436).

The Applicant demonstrated substantial evidence of Abilify Mycite usability in one simulated use trial involving the intended population. When used in conjunction with the Medical Information Device #1 (MIND1) system, 90% of aripiprazole + IEM ingestions are detected within 30 minutes and 97% of aripiprazole + IEM ingestions are detected within two hours by the wearable sensor. Detection is accurately communicated to both the Mycite mobile application and the clinician/caregiver web-portal.

(b) (4). Rates of adherence to the MIND1 system noted during the first review cycle were no different than rates of adherence noted in real-world adherence trials for daily oral antipsychotics.[1] The simulated use trial performed for the re-submission provides no additional data regarding adherence or data regarding data transmission times. Considering these limitations, the most accurate statement regarding Abilify Mycite's capabilities is that "Abilify Mycite successfully tracks ingestion of aripiprazole with embedded sensor."

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Schizophrenia, Bipolar disorder, and Major Depressive Disorder (MDD) are serious and common mental disorders in the United States. Depressive disorders account for 40.5% of the disability caused by mental illness worldwide. In 2014, an estimated 15.7 million adults [6.7% of the adult population] in the United States had at least one major depressive episode in the past year. The estimated prevalence for schizophrenia and bipolar disorder in the U.S. population is roughly 1% and 3%, respectively.

Poor patient adherence to pharmacological treatment is common in this patient population.[1] All three disorders commonly require long-term or lifelong adherence to daily treatment to avoid relapse. Epidemiologic and clinical trials observe that relapse through non-adherence decreases rates of response to treatment, particularly response to previously effective drugs. While once widely accepted that parenterally administered depot antipsychotics improved treatment adherence, recent trials cast doubt upon this assertion. Newer trials suggest parentally administered depot antipsychotics merely delay non-adherence.[2-4] However, depot antipsychotics maintain the advantage of predictable timeframes in which clinicians and caregivers know repeat dosing is required and intervene accordingly. Adherence to depot

antipsychotics is also relatively easy to monitor, as clinicians know when they last administered the injection. Currently, seven FDA-approved, long-acting antipsychotic products exist. These include long-acting forms of haloperidol, fluphenazine, risperidone, paliperidone, aripiprazole, aripiprazole lauroxil, and olanzapine. Required frequency of long-acting parenteral antipsychotic administration ranges from weekly to quarterly.

Abilify Mycite adds to the current treatment armamentarium for schizophrenia and mood disorders by allowing clinicians and caregivers another way to track aripiprazole ingestion, provided the right type of patient receives the product. Aripiprazole + MIND1 is not uniquely efficacious compared with other approved treatments and potential benefits decrease if prescribed to non-compliant, cognitively challenged, or oppositional patients.

Mitigation of risks associated with delay in data transmission and wearable sensor-related adverse events are achieved through labeling. Mitigation of unanticipated risks associated with unstudied functions of the mobile application are achieved through the placement of a disclaimer statement in labeling and the mobile application. For regulatory purposes, the mobile application and web-portal are considered drug labeling. The required disclaimer will remind users and prescribing clinicians that drug ingestion is the only function of the mobile application that has been reviewed by the FDA. I recommend approval of the proposed product after obtaining agreement from the Applicant regarding the incorporation of a disclaimer statement into Limitations of Use (LOU). LOUs are required to appear in traditional labeling, the log-in screen for the mobile application, the log-in screen for the web-portal, and the summary screen of the web-portal.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Schizophrenia, Bipolar disorder, and Major Depressive Disorder are serious and common mental disorders in the United States. • Depressive disorders account for 40.5% of the disability caused by mental illness worldwide. In 2014, an estimated 15.7 million adults in the United States had at least one major depressive episode in the past year. • Sustained remission from symptoms for each of these disorders often requires polypharmacological treatment.	• Epidemiologic and clinical trials observe that relapse through non-adherence decreases rates of response to treatment, particularly response to previously effective drugs. • The need for polypharmacological treatment is likely reduced when patients are adherent to prescribed antipsychotics.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Poor patient adherence to pharmacological treatment is common in this patient population.[1] • All three disorders commonly require long-term or lifelong adherence to daily treatment to avoid relapse.	• Expanding interventions that potentially improve adherence to prescribed antipsychotics is critically important to the public health.
Current Treatment Options	• FDA-approved long-acting formulations of antipsychotic drugs include haloperidol, fluphenazine, risperidone, paliperidone, aripiprazole, aripiprazole lauroxil, and olanzapine. • Required frequency of long-acting parenteral antipsychotic administration ranges from weekly to quarterly. • Administration of a long-acting antipsychotic requires a trained clinician for administration and post-injection monitoring. • Adherence to depot antipsychotics is relatively easy to monitor, as clinicians know when they administered the injection. • FDA-approved oral formulations of antipsychotic drugs include chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, perchloroperazine, thioridazine, thiothixene, trifluoperazine, aripiprazole, asenapine, clozapine, illoperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone.	• While once widely accepted that parenterally administered depot antipsychotics improved treatment adherence, recent trials cast doubt upon this assertion. Newer trials suggest parentally administered depot antipsychotics merely delay non-adherence. • The advantage of using long-acting antipsychotics is the predictable timeframe in which clinicians and caregivers know repeat dosing is required.
Benefit	• Abilify Mycite provides a means of tracking oral aripiprazole ingestion. • Long-term adherence to oral antipsychotic drugs is poor. • Many patients struggling with adherence to antipsychotic drugs cannot receive or refuse to receive long-acting antipsychotic drugs.	• Potential for improved adherence to oral aripiprazole is possible with Abilify Mycite use. • Adverse effects associated with oral aripiprazole are time-limited whereas adverse events associated with long-acting antipsychotics are prolonged. • Approval will likely spur future innovation

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		of similar drug tracking technology. • Potential for improved communication between patients and clinicians regarding treatment is possible with Abilify Mycite.
Risk	• Individuals with active symptoms of schizophrenia, bipolar disorder, and major depressive disorder are more likely to use Abilify Mycite incorrectly. • Minor, self-limited adverse events associated with the wearable sensor were common in the three repeat-dose clinical trials, accounting for 32%, 34%, and 64% of reported adverse events. • Rare, severe dermatologic reactions requiring days to weeks to resolve occurred. • Infections accounted for a higher than predicted 9%, 11%, and 18% of reported adverse events in the three repeat-dose trials. Infection rates are not reported in initial placebo-controlled published aripiprazole tablet clinical trials; rates are assumed to be <2%. Raw data from these initial trials is contained in unavailable paper records.	• Usage errors increase the likelihood of patients experiencing wearable sensor-related adverse events and overdose. • Significant harm from usage errors is unlikely. Aripiprazole is relatively non-toxic in overdose and patients will presumably remove the wearable sensor if an adverse event occurs. • Rates of infection in repeat-dose trials are explainable by high rates of concomitant antipsychotic use. It is likely that Abilify Mycite is not associated with a higher rate of infection than is present with aripiprazole.
Risk Management	• The longest Abilify Mycite trial was 16 weeks in length. • The generalizability of the applicant's two-day simulated use trial to real-world Abilify Mycite use over time is unknown. • While the overwhelming majority of tablets are detected within an hour or less post-ingestion, a delay of up to four hours in transmission of data from aripiprazole + IEM tablet to the Mycite mobile application and clinician/caregiver web-portal occurred in outlying cases.	• An open-label, longitudinal post-marketing trial evaluating rates of correct MIND1 use, rates of wearable sensor-related adverse events, rates of MIND1-related overdose, rates of MIND1 adherence, and rates of infection in individuals using the MIND1 system is recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Correct Abilify Mycite use in the simulated use trial was 66%. • Combining individuals who correctly used the product with individuals that failed in ways that did not undermine aripiprazole tablet ingestion, 86% of enrolled participants derived benefit from ingesting aripiprazole as prescribed. • Minor, self-limited wearable sensor-related adverse events occurred frequently in Abilify Mycite clinical trials. • Rare, severe dermatologic reactions requiring days to weeks to resolve occurred.	• The Division recommended specific criteria for wearable sensor discontinuation in labeling. • Specific language cautioning against "real-time" use of Abilify Mycite is incorporated into labeling.

2 Therapeutic Context

2.1. Analysis of Condition

Please see *Section 1.3 Risk Benefit Assessment* for condition details pertaining to this application.

2.2. Analysis of Current Treatment Options

Please see *Section 1.3 Risk Benefit Assessment* for current treatment details pertaining to this application.

Table 1: Summary of FDA-Approved Long-Acting Antipsychotics

Product (s) Name	Relevant Indication	Dosing/ Administration
haloperidol decanoate	Schizophrenia	50mg or 100mg injection monthly
fluphenazine decanoate	Schizophrenia	12.5mg to 100mg injection monthly
risperidone	Schizophrenia and Bipolar I Disorder	12.5mg, 25mg, 37.5mg, or 50mg injection every two weeks
paliperidone palmitate (1-month formulation)	Schizophrenia and Schizoaffective Disorder	39mg, 78mg, 117mg, 156mg, or 234mg injection monthly
paliperidone palmitate (3-month formulation)	Schizophrenia	273mg, 410mg, 546mg, or 819mg injection quarterly
aripiprazole	Schizophrenia and Bipolar I Disorder	300mg or 400mg injection monthly
aripiprazole lauroxil	Schizophrenia (b) (4) (b) (4)	441mg, 662mg, or 882mg injection monthly; 882mg injection every six weeks; 1064mg injection every two months
olanzapine pamoate	Schizophrenia	150mg-300mg injection every two weeks; 405mg injection monthly

Source: Reviewer Constructed

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Approved aripiprazole formulations include oral tablets, oral solution, oral disintegrating tablets, intramuscular injectable, and multiple formulations of extended-release injectable.

Aripiprazole Indications by Year Granted	
Schizophrenia	2002
Acute bipolar disorder	2004
Bipolar disorder maintenance	2004
Adjunctive treatment of bipolar disorder	2004
Adjunctive treatment of major depressive disorder	2007
Irritability in children with autism	2009
Agitation associated with bipolar I mania and schizophrenia	2009

3.2. Summary of Pre-Submission/Submission Regulatory Activity

During the original review cycle, reviewers identified several quality deficiencies. The Division issued a Complete Response letter, dated April 26, 2016. In Trial #316-13-206b, reviewers noted data for placebo only, significant non-detection of dosing 30 minutes following ingestion, (b) (4) Reviewers observed wide variability in time to data transmission from the wearable sensor to the Cloud server and mobile application. As no transmission times involved the fed state, reviewers did not know if food influenced variability for transmission times. Together, these concerns formed the basis for the Complete Response action.

In the Complete Response letter, FDA required the Applicant undertake a trial designed similarly to Trial #316-13-206b *"unambiguously testing the to-be-marketed formulation under real world conditions."* FDA also asked that the Applicant incorporate safeguards (b) (4) . The Complete Response letter offered removal of the (b) (4) from the mobile application as an alternative way to satisfy this requirement.

Following the Complete Response letter, the Applicant submitted a human factors protocol for FDA review on September 19, 2016. The FDA completed an a priori review of the protocol on December 23, 2016. After receiving feedback on the protocol, the Applicant conducted a 35 participant, two-day simulated use trial (DC-001576) at three U.S. sites from February 21, 2017, to March 3, 2017. The Applicant also removed the (b) (4) from the mobile application.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

FDA conducted no inspections in response to re-submission of this application.

4.2. Product Quality

From the perspective of product quality, the Applicant adequately responded to all deficiencies laid out in the Complete Response letter.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable.

4.5. Clinical Pharmacology

Not applicable.

4.5.1. Mechanism of Action

Aripiprazole is a dihydroquinolinone antipsychotic with no psychoactive metabolites. Pharmacologically, aripiprazole exhibits partial affinity at D_2 and $5HT_{1A}$, antagonism activity at $5HT_{2A}$, and affinity at D_3, D_4, $5HT_{2C}$, $5HT_7$, α-1, and H_1.

4.5.2. Pharmacodynamics

The Applicant successfully demonstrated bioequivalence between approved oral aripiprazole tablets (the reference product) and oral aripiprazole tablets with embedded IEM in the original submission dated Jun 26, 2015.

4.5.3. Pharmacokinetics

The Applicant successfully demonstrated bioequivalence between approved oral aripiprazole tablets (the reference product) and oral aripiprazole tablets with embedded IEM in the original submission dated Jun 26, 2015.

4.6. Devices and Companion Diagnostic Issues

The MIND1 system received FDA approval on April 21, 2016 [Drug Master File (DMF) 29332]. At that time, FDA confined approval to placebo + IEM only.

Office of Medical Products and Tobacco (OMPT) and Office of Prescription Drug Promotion (OPDP) were most concerned with the construction of the mobile application. The Applicant submitted no data suggesting that the patient-rated mood, patient-rated rest, and pedometer functions contained within the mobile application lead to better care or improve patient outcomes. Functions unrelated to tracking ingestion were not reviewed by FDA.

The review team had concerns regarding the inclusion of unstudied functions within the mobile application. These concerns resulted in a Medical Policy and Program Review (MPPR) Committee meeting on the PDUFA due date, October 20, 2017. A summary of the MPPR meeting is found in *Section 9 Advisory Committee Meeting and Other External Consultations*.

4.7. Consumer Study Reviews

DMEPA determined that the Applicant successfully mitigated their concerns related to human factor error in the simulated use trial [DC-001576].

5 Sources of Clinical Data and Review Strategy

Table 2: Table of Clinical Studies

***Note: Trials other than DC-001576 underwent review during the first review cycle**

Phase	Trial	Participants	Trial Design	Duration
4	316-13-204	58 adults with bipolar disorder or major depressive disorder	open label, single arm	16 weeks
1	316-13-205	30 healthy adults	randomized, open label, controlled	28 days
4	316-13-206a	30 healthy adults	open label, single arm	1 day
4	316-13-206b	29 healthy adults	open label, single arm	1 day
2	316-13-215	49 adults with schizophrenia, bipolar I disorder, or major depressive disorder	open label, single arm	2 days
2a	316-14-220	67 adults with schizophrenia	open label, single arm	8 weeks
4	DC-001576	35 adults with schizophrenia, bipolar I disorder, or major depressive disorder	open label, simulated use trial	2 days

5.1. Review Strategy

Previous review of six of the seven trials took place during the initial application. However, the first review did not raise one important safety-related issue, warranting a limited second review of these trials.

Review of new material submitted focused entirely on patient ability to use the MIND1 system successfully and potential clinical implications of task difficulties, close calls, and failures observed.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. MIND1 System 2016 Human Factors Patient Interface Validation [DC-001576]

6.1.1. Study Design

Overview and Objective

The Applicant conducted DC-001576 to validate safe and effective MIND1 use within the intended population using the to be marketed kit intended for commercial sale. DC-001576 was a two-day simulated use trial evaluating the (b) (4), the wearable sensor, the mobile application, draft labeling, packaging, and packaging inserts. Drug Evaluation and Medical Error Prevention (DMEPA) completed a companion review of this trial as well.

Trial Design

Thirty-five adults diagnosed with major depressive disorder, bipolar I disorder, or schizophrenia simulated repeated use of Abilify Mycite on two consecutive days. Participants did not ingest actual drug product. Instead, participants placed tablets in containers to simulate ingestion. Participants affixed wearable sensors to a protective covering the intended placement site on the skin. In both sessions, investigators assessed the participant's ability to complete critical and necessary tasks for safe and effective use of Abilify Mycite.

On Day 1, participants took part in a "study session" lasting up to 75 minutes with the option to extend the session's duration if the participant needed more time to complete tasks or the moderator needed more time to probe difficulties, close calls, or failures. All participants viewed instructional videos contained with the mobile application during the "study session." If a participant left without completing one or more task(s), task completion took place on Day 2. Configuration of the MIND1 system for first time use occurred only on Day 1. Seventeen

participants received assistance in configuring the MIND1 system for first time use and eighteen received no help.

On Day 2, participants again took part in a "study session" lasting up to 75 minutes and viewed instructional videos before simulating ongoing use of Abilify Mycite, completing assessment trials, and assisting investigators with root case analyses of all failures, close calls, and difficulties.

Study Endpoints

Primary Endpoints: Frequency of failure, close calls, and difficulty in completing pre-specified tasks required for safe and effective Abilify Mycite use.

Secondary Endpoints: Root causes of observed failures, close calls, and difficulty in completing pre-specified tasks required for safe and effective Abilify Mycite use.

Protocol Amendments

The Applicant submitted no amendments to the protocol after incorporating FDA feedback into the final protocol.

Data Quality and Integrity: Applicant's Assurance

The Applicant collected all data on site using the discussion guide and digital data collection spreadsheet. The moderator and notetaker independently completed these documents during each interview. The moderator and notetaker collected data on all steps of use. Data collected included primary endpoint data, whether a task was attempted, and unanticipated use errors. The moderator also recorded reasons for performances problems. Investigators utilized a human factors tool to ensure correct task set up and assist with identification of deviations. The Applicant entered all data into a controlled document management system allowing for full version control and change history traceability. The CRO archived hard copies of all data produced. The Applicant mitigated missing data by consulting the dual electronic and paper records. If this could not resolve the missing data, video footage of the session was used.

6.1.2. Study Results

Compliance with Good Clinical Practices

During the original application, CMC noted that Proteus failed to document use of Good Clinical Practices in animal trials. Confirmation of failure to use Good Clinical Practices occurred when FDA requested further information.

During the original application, CMC also inspected the Applicant's second Tokushima factory in

Japan and found numerous deficiencies, which were noted in the Complete Response letter. The Applicant subsequently addressed these deficiencies to CMC's satisfaction.

Trials involved no debarred investigators under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992.

Financial Disclosure

The Applicant made no financial disclosures for DC-001576. During the original review cycle, the Sponsor reported one disclosable investigator financial interest. (b) (6) (Trial (b) (6)) reported making over $25,000 a year from speaking fees. Given that (b) (6) was a blinded investigator and held no personal stake in the success of Abilify Mycite, this likely had no impact on results on obtained.

Patient Disposition

The trial population consisted of 18 individuals randomized to no assistance in configuring the mobile application for first use, 17 individuals randomized to receiving assistance in configuring the mobile application for first use, and two individuals disqualified after enrollment. Investigators disqualified one individual for not being an iPhone user and the other for requesting to withdraw from the trial after Day 1. All non-disqualified participants completed the trial and comprise the trial population for purposes of analysis. ITT was not considered a valid method of dealing with missing data due to the nature of data being collected.

Protocol Violations/Deviations

The Applicant intended to conduct 15 cautionary statement assessments. However, the protocol did not specify this separate sample size requirement because the Applicant intended for participants to complete all assessments. Operating under this assumption, the Applicant incorporated no randomization or counterbalancing plan into the protocol to ensure even distribution of cautionary statement questions across participants. The lower sample size on seven statements is a technical deviation from the protocol as worded, despite consistency with protocol intent. This deviation did not impact results.

Table 3: Demographic Information Tracked by Applicant

	N	Schizophrenia	Bipolar I Disorder	MDD	Mean Age (Range)	Right Handed	Left Handed	No Glasses	Glasses
Overall	35	12	12	11	37.1 (19-63)	33	2	21	14
Assisted	17	6	6	5	38.9 (20-63)	16	1	9	8
Unassisted	18	6	6	6	35.4 (19-63)	17	1	12	6

Abbreviations: Major Depressive Disorder (MDD)
Source: Reviewer Constructed.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

In addition to requiring that participants have a confirmed diagnosis of major depressive disorder, bipolar I disorder, or schizophrenia, the Applicant required that participants have a Clinical Global Impression-Severity of ≤4. Scores in this range indicate exclusion of individuals with greater than moderate severity.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not applicable.

Efficacy Results – Primary Endpoint

Most participants used the MIND1 system correctly. By trial's end, 23 of 35 participants (66%) demonstrated correct use of Abilify Mycite. This represents improvement from the first review cycle where participants demonstrated 52% correct use after eight weeks.

Most task failures reported render the MIND1 system ineffective without resulting in serious harm or interfering with tablet ingestion. This also improves upon data submitted during the first review cycle. Specific failures observed that do not impact aripiprazole tablet ingestion include failure to apply the initial wearable sensor, failure to apply a replacement wearable sensor, failure to download the mobile application, and failure to peel the large tab.

Other reported task failures carry a theoretical risk of overdose or dermatologic reaction. Theoretical risk exists for participants ingesting a second tablet based on receiving incorrect data, experiencing wearable sensor failure from excessive wear of the sensor, or experiencing a

dermatologic reaction from excessive wear of the sensor. Such failures include acting on the summary tile that displayed data from the previous day, failure to remove the wearable sensor, failure to pair the replacement wearable sensor, ingesting the first tablet before applying the wearable sensor, forgetting to take the tablet, not checking 0-day status to ensure device functionality, failure to understand why a tablet does or does not register with MIND1 system, and believing the MIND1 system tracked ingestion of drugs other than aripiprazole + IEM. In total, five of 35 participants (14%) failed in tasks associated with these theoretical risks.

Table 4: Listing of All Participant Failures in DC-001576

Participant	Group Assignment	Condition	Failure 1	Failure 2	Failure 3	Failure 4
(b) (6)	Assisted	BP1	Acted on Summary Tile	-	-	-
	Assisted	BP1	Did Not Remove Wearable Sensor	Did Not Apply Replacement Wearable Sensor	Acted on Summary Tile	Did Not Check Expiration Date
	Assisted	BP1	Pill Did Not Register	-	-	-
	Assisted	BP1	Did Not Understand Only MIND1 Pills Work with System	Did Not Understand the Need to Change Wearable After One Week	-	-
	Unassisted	BP1	Pill Did Not Register	-	-	-
	Unassisted	SCZ	Did Not Apply Wearable Sensor Correctly	Did Not Apply Replacement Wearable Sensor Correctly	Ingested First Pill Before Setting Up System	-
	Unassisted	SCZ	Did Not Pair Replacement Wearable Sensor Correctly	-	-	-
	Assisted	SCZ	Did Not Pair Replacement Wearable Sensor Correctly	-	-	-
	Unassisted	SCZ	Did Not Download App	Did Not Remove Large Tab from Wearable Sensor	Did Not Check 0-day Status	Ingested First Pill Before Setting Up System
	Unassisted	MDD	Did Not Pair Replacement Wearable Sensor Correctly	-	-	-
	Unassisted	MDD	Did Not Apply Wearable Sensor Correctly	-	-	-

Abbreviations: Bipolar I Disorder (BP1), Schizophrenia (SCZ), Major Depressive Disorder (MDD)
Source: Reviewer Constructed

Data Quality and Integrity – Reviewers' Assessment

Not applicable.

Efficacy Results – Secondary and other relevant endpoints

Two clear themes emerged from the root cause analysis. Most task failures occurred due to either literal interpretation of the initial investigator instruction to "do what you would do at home" or occurred due to participant poor impulse control.

Participants interpreting the instruction literally reported variations of the following composite statement: "I don't use an app when I take my medications at home, so I didn't do it here. I only take my pill at home." Thus, labeling discussions occurred with careful attention to this issue.

Impulsive participants opened the packaging all at once before receiving guidance. In doing so, these participants bypassed the conscious step-by-step ordering of materials within the packaging. These participants universally failed to take notice of directions to view an online training video prior to using the product. Many applied the wearable sensor incorrectly or simulated ingestion of the tablet incorrectly based on their prior understanding of how patches and pills typically function. This observation received thorough examination in the DMEPA review, but did not directly impact the clinical review.

Dose/Dose Response

Not applicable.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

6.2. Trials Reviewed During the First Review Cycle

6.2.1. Confounding in Repeat-Dose Trials

- Safety data for repeat-dose trials is confounded due to many participants receiving concomitant antipsychotic(s). An in-depth discussion of this issue is located in *Section 8.4.1 Infection Risk*.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Sections 7.1.1-7.1.5 were deleted because the submitted trial contained no efficacy data.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post-Market Setting

As mentioned in the risk/benefit analysis, the generalizability of the applicant's two-day simulated use trial to real-world Abilify Mycite use over time is unknown. Based on safety signals of unknown significance observed in submitted trials, post-marketing surveillance focused on rates of correct MIND1 use, rates of wearable sensor-related adverse events, rates of MIND1-related overdose, rates of MIND1 adherence, and rates of infection in individuals using the MIND1 system would be beneficial.

7.2.2. Other Relevant Benefits

The mobile application and web-portal allow for verification of drug ingestion by Sponsors conducting clinical drug trials and by caregivers of severely ill patients in addition to clinicians and patients as previously discussed.

7.3. Integrated Assessment of Effectiveness

The submitted trial contained no efficacy data.

8 Review of Safety

The one new trial in this application included no safety data. Prior safety data underwent review during the first review cycle. For details regarding Trials 316-13-204, 316-13-205, 316-13-206a, 316-13-206b, 316-13-215, and 316-14-220, please see the first clinical review of this

product by Paul Andreason, dated April 26, 2016. One new safety issue is raised in this review regarding previously submitted trials. Please see *Section 8.4.1 Infection Risk* for details regarding the potential increased risk of infection with Abilify Mycite.

8.1. Safety Review Approach

The submitted trial contained no safety data.

8.2. Adequacy of Applicant's Clinical Safety Assessments

8.2.1. Issues Regarding Data Integrity and Submission Quality

A technical problem with the adverse event dataset prevented me from being able to analyze adverse event data using software programs. Ultimately, I could extract and analyze the adverse event data.

8.2.2. Categorization of Adverse Events

I noted concerns related to infection and wearable sensor-related adverse events after combining low level MedDRA terms describing similar adverse events such as "rash due to wearable sensor" and "wearable sensor-related adverse event." I noted that coding of low level MedDRA terms into standard MedDRA terms was done correctly for most adverse events.

8.2.3. Routine Clinical Tests

The submitted trial contained no safety data.

8.3. Safety Results

The submitted trial contained no safety data.

8.3.1. Infection Risk

For details regarding Trials 316-13-204, 316-13-205, 316-13-206a, 316-13-206b, 316-13-215, and 316-14-220, please see the first clinical review of this product by Paul Andreason, dated April 26, 2016.

An additional safety concern not raised in the original review involves the higher than expected rate of infection observed for participants exposed to Abilify Mycite. The table below displays rates of infection noted in repeat-dose trials. Historic rates of infection-related adverse events noted in adult oral aripiprazole trials are presumed to be <1% because of their omission from medical journal publications. Definitive determinations about infections in the original

aripiprazole trials cannot be made because physical copies of their NDA submissions are unavailable.

Definitive conclusions regarding infection data cannot be made due to confounding. Potential explanations for this observation include: (1) potential immunosuppressant effects of concomitant antipsychotics, (2) potential artifact stemming from the population studied, or (3) potential immunosuppression secondary to chronic exposure to the components of the IEM and wearable sensor, such as (b) (4) gold. This warrants attention during post-marketing surveillance to clarify if Abilify Mycite increases the risk of infection or this observation occurred due to factors inherent to the clinical trials.

Table 5: Rates of Infection Noted in Repeat-Dose Abilify Mycite Trials

	Trial #316-13-204	Trial #316-13-215	Trial #316-14-220
Total N	**58**	**49**	**67**
# of Reported Infection-Related AEs	**14 (18%)**	**3 (9%)**	**4 (11%)**
% on Concomitant Neuroleptics	**41%**	**Not Tracked**	**24%**
Specific Infections Noted	**bacteremia (1), fungal infection (1), gastroenteritis (2), tooth or gum infection (2), nasopharyngitis (2), cellulitis (1), sinusitis (1), URI (3), UTI (1)**	**sinusitis (1), URI (2)**	**nasopharyngitis (1), URI (3)**

Source: Reviewer Constructed

Safety subsections "Deaths" Through "Overdose, Drug Abuse Potential, Withdrawal, and Rebound" were deleted because the one new trial in this application included no safety data.

8.4. Safety in the Post-Market Setting

8.4.1. Safety Concerns Identified Through Post-Market Experience

Not Applicable. The proposed product is not approved for sale in the U.S.

8.4.2. Expectations on Safety in the Post-Market Setting

The most recent trial involved only two days of simulated product use. Generalizability of this trial to use in the general population is unknown. Based on safety signals of unknown significance observed in submitted trials, post-marketing surveillance focused on rates of correct MIND1 use, rates of wearable sensor-related adverse events, rates of MIND1-related overdose, rates of MIND1 adherence, and rates of infection in individuals using the MIND1 system would be beneficial.

8.5. Additional Safety Issues from Other Disciplines

Not applicable.

8.6. Integrated Assessment of Safety

The submitted trial contained no safety data.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meetings or external consultations occurred during the re-submission. The regulatory briefing that occurred during the first review cycle is described in detail in the initial clinical review, dated April 26, 2016.

A MPPR took place regarding the proposed product on October 20,2017. The MPPR discussed regulatory issues related to inclusion of the rest, mood, and pedometer functions within the mobile application. CDER leadership concluded that the proposed product could be approved without removing these functions from the mobile application provided the Applicant agreed to place appropriate disclaimer statements in labeling and the mobile application itself. Center for Drug Evaluation and Research (CDER) leadership prioritized facilitating the addition of an appropriate disclaimer statement into the LOUs and approving the proposed drug product during this review cycle over meeting the PDUFA deadline.

10 Labeling Recommendations

10.1. Prescribing Information

During negotiation with the Applicant, agreement was reached regarding disambiguation of

MIND1 component names in labeling, removal of potentially promotional language from labeling, the proposed product's indications for use, and the inclusion of LOUs in labeling, the mobile application, and the clinician web-portal.

Disclaimer statement and LOU verbiage were being negotiated at the time this review was finalized. Draft language for the disclaimer statement and LOU at the time of this review read as follows:

Draft Disclaimer Statement

"(b) (4)], only the function related to tracking medication ingestion has been evaluated by FDA.(b) (4)

Draft LOU Statements

- 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.

(b) (4)

10.2. Patient Labeling

The draft disclaimer statement and draft LOU statements were in the process of being converted into patient-friendly language at the time this review was finalized.

10.3. Non-Prescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not indicated. Risks can be mitigated appropriately through previously discussed labeling and LOUs.

Post-Marketing Requirements and Commitments

No post-marketing requirements or commitments were indicated.

Based on safety signals of unknown significance observed in submitted trials, post-marketing surveillance focused on rates of correct MIND1 use over time, rates of wearable sensor-related adverse events, rates of MIND1-related overdose, rates of MIND1 adherence, and rates of infection in individuals using the MIND1 system would be beneficial.

12 Appendices

12.1. References

1. Alphs, L., et al. (2015). "Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study." J Clin Psychiatry 76(5): 554-561.
2. Fu DJ, Bossie CA, Sliwa JK, et al. Paliperidone palmitate versus oral risperidone and risperidone long-acting injection in patients with recently diagnosed schizophrenia: a tolerability and efficacy comparison. Int Clin Psychopharmacol 2014;29:45-55.
3. McEvoy JP, Byerly M, Hamer RM, et al. Effectiveness of paliperidone palmitate vs. haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. JAMA 2014;311:1978-87.
4. Markowitz M, Fu DJ, Levitan B, et al. Long-acting injectable paliperidone palmitate versus oral paliperidone extended release: a comparative analysis from two placebo-controlled relapse prevention studies. Ann Gen Psychiatry 2013;12:22.

12.2. Financial Disclosure

The Applicant made no financial disclosures in the resubmission. During the first review cycle, the Applicant reported one disclosable investigator financial interest. (b) (6) (Trial (b) (6)) reported making over $25,000 a year from speaking fees.

Covered Clinical Study (Name and/or Number): DC-001576

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in S Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

DANIEL J LEE
10/26/2017

JAVIER A MUNIZ
10/27/2017

Cross-Discipline Team Leader Review

Date	4/25/16
From	Tiffany R Farchione, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	207202
Applicant	Otsuka Pharmaceutical Company Ltd.
Date of Submission	6/26/2015
PDUFA Goal Date	4/26/2016
Proprietary Name / Non-Proprietary Name	Abilify MyCite
Dosage form(s) / Strength(s)	Oral Tablet 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30
Applicant Proposed Indication(s)/Population(s)	(b) (4) as indicated for schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of major depressive disorder. (Adult patients)
Recommendation on Regulatory Action	Complete Response

1. Introduction

This application is the first of its kind. The applicant, Otsuka Pharmaceutical Company Ltd. (hereafter, "Otsuka" or "the applicant"), is seeking approval of a drug-device combination in which their product, aripiprazole (Abilify, NDA 21436) is combined with a 510(k)-cleared device manufactured by Proteus Digital Health (hereafter, "Proteus"). Aripiprazole is indicated for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of major depressive disorder (MDD); the Proteus device includes an ingestible sensor or event marker (IEM) and a wearable patch to detect when the IEM has been ingested. The product under review includes the IEM imbedded within aripiprazole tablets, the wearable patch, a medical device data system (MDDS) that runs on the patient's smartphone, and a smartphone app developed by Otsuka. Used together, the applicant claims that this system (known as "MIND1" during development) will allow patients in the currently-indicated populations listed above (b) (4) if the patient chooses, he or she can allow others (e.g., physician, family members) to view the information recorded by the patch as well.

2. Background

Oral aripiprazole was first approved in November, 2002, with an initial indication for the treatment of schizophrenia. It is also approved for the acute treatment of manic or mixed episodes associated with bipolar I disorder (as monotherapy and as an adjunct to lithium or valproate), and for adjunctive treatment of MDD; additional pediatric indications include irritability (not agitation, as stated in the clinical review) associated with autistic disorder, and Tourette's disorder. The applicant is only seeking to include information related (b) (4) schizophrenia, bipolar I, and adjunctive treatment of MDD in this product's labeling.

Proteus received 510(k) clearance in February, 2014, for a device called the Proteus Patch Including Ingestible Sensor. The Proteus device consists of the IEM, a wearable patch with embedded software, and an MDDS that runs on the patient's smartphone. The patient applies the patch to his or her body; it then collects physiological and behavioral data such as heart rate, activity, body angle relative to gravity, and time-stamped user-logged events generated by swallowing the ingestible sensor. The sensor is embedded inside a tablet for ease of swallowing. Once the ingestible sensor reaches the stomach, it activates and communicates its presence and unique identifier to the patch. The patch stores and wirelessly (via Bluetooth) sends the physiological, behavioral, event, and ingestion data to the MDDS. The Proteus system has been cleared using the product code OZW under the following 510(k) submissions:

- K113070/DEN120011
- K131009
- K131524
- K133263
- K150494

3. CMC/Device

The Office of Pharmaceutical Quality (OPQ) review was conducted by the following team of reviewers:

DISCIPLINE	REVIEWER
Drug Substance & Drug Product	Mariappan Chelliah
Process and Microbiology	Hang Guo
CDRH Lead Reviewer	Luke Ralston
Facility	Donald Obenhuber
Biopharmaceutics	Gerlie Gieser
RBPM	Grafton Adams & Dahlia Woody
Application Technical Lead	David Claffey

OPQ recommends a Complete Response action for this application. The OPQ review notes a number of deficiencies. The reviewers have generally made approval recommendations based on the performance of the system's individual components; however the proposed product is designed to work as an integrated combination product. The reviewers conclude that the in vivo performance of the final commercial product (i.e., the drug-device combination system of aripiprazole, the IEM, the patch, and the smartphone app) has not been adequately demonstrated.

The reviewers also note that, although the proposed indication is to (b) (4)

The Osmitter 316-13-206B study is intended to demonstrate the reliability of the system; however, placebo tablets rather than the commercial tablets were used in this study. Given the risk of dosing errors, OPQ could not bridge the data to predict how the product will perform on the market in the patient's hands given:

- the novelty and lack of commercial experience with this class of product,
- the known in vitro IEM performance differences between tablet strengths/sizes,
- the marginally adequate detection accuracy and inconsistent lag time results of the Osmitter 316-13-206B study, and
- the idealized study conditions of Osmitter 316-13-206B.

OPQ recommends that the Applicant carry out a similar study to unambiguously test the to-be-marketed formulation under the conditions in which it is likely to be used. They request that the study have a predetermined and justified endpoint, e.g., positive detection rate after a certain

time period. They also recommend that the tablets studied represent or bracket the commercial tablet sizes/strengths, that the Applicant study ingestion both with and without food, and that the Applicant consider using aged tablets in the study.

OPQ also states that should the applicant redesign the app (b) (4) . (b) (4) The risk of dosing errors would also be reduced (b) (4) In the context of this reduced risk, OPQ believes the 206B studies could potentially support the adequacy of the product's performance, though this will require reevaluation in the context of future changes in the app.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this application.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology information was submitted with this application.

The biopharmaceutics review focused on the evaluation of (1) the biowaiver request for all the proposed strengths of aripiprazole + IEM tablets, (2) the proposed dissolution method and acceptance criterion, and the (3) adequacy of the bridging information provided for the primary stability and the proposed commercial batches of the aripiprazole + IEM tablets. The biopharmaceutics reviewer determined that the in vitro dissolution test and acceptance criteria are adequate for assuring quality control and consistent bioavailability of the drug product.

6. Clinical Microbiology

No clinical microbiology information was submitted with this application.

7. Clinical/Statistical-Efficacy

The Applicant submitted data from the following studies to support this application:

- 316-13-204: A Formative Usability Study of the Otsuka MIND1 Prototype by Subjects with Bipolar Disorder or Major Depressive Disorder United States
  - This was an open-label, single-arm, 16-week study in which 58 subjects with either bipolar disorder or MDD were recruited (47 completers) to provide feedback about the use of the MIND1 System and any application (i.e., software) updates that were made during the trial.
  - The secondary objective of this trial was to characterize the safety of the MIND1 System.

- The tertiary objectives were to summarize the subject cohort's medication-taking adherence based on IEM detections reported by the MIND1 System and to summarize adhesive and other user behaviors for the patch.
- Usability evaluation was assessed using feedback from subject and caregiver questionnaires on the use of the MIND1 System. Descriptive feedback on the usability of the mobile and web application (i.e., Otsuka app) to include mood, rest, activity, ingestion, and other related features of the MIND1 System was collected.
- In brief, at the last trial visit, 88.2% of the subjects agreed that the Otsuka app was easy to use, 68.6% of subjects felt it was comfortable to wear the patch, 74.5% of subjects and 78.6% of caregivers reported that they felt satisfied with the MIND1 System, and 74.5% of subjects and 72.0% of caregivers reported they would be interested in using the MIND1 System in the future.

- 316-13-206a: OSMITTER 316-13-206A: A Substudy to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Period
  - This was an open-label, single-arm, single day study in 30 healthy volunteers.
  - The primary objective of this study was to measure the accuracy of ingestible event marker (IEM) detection by the MIND1 System using both aripiprazole-embedded IEM tablets and the placebo-embedded IEM tablets, and to evaluate the latency period between ingestion and detection for both ingestions.
  - This trial used the (b) (4) version of the IEM; the (b) (4) is the current version of the IEM.
  - This trial was conducted to determine the accuracy of IEM detection by completing a series of patch applications and IEM ingestions in the clinic. The study subjects were not responsible for any aspect of patch placement, pairing to the mobile device, data interpretation, or troubleshooting.
  - Following placement of the patch by clinic staff, subjects ingested one IEM tablet approximately every 2 hours, for a total of 4 ingestions. The subjects ingested one 10-mg aripiprazole-embedded IEM (aripiprazole + IEM) tablet without food (Hour 0), one placebo-embedded IEM (placebo + IEM) tablet without food (approximately Hour 2), one placebo + IEM tablet with a high-fat meal (approximately Hour 4), and one placebo + IEM tablet without food (approximately Hour 6).
  - The Otsuka app recorded 76.7% (92/120) of IEM ingestions overall.
    - Hour 0: 73.3% (22/30 ingestions)
    - Hour 2: 63.3% (19/30 ingestions)
    - Hour 4: 76.7% (23/30 ingestions)
    - Hour 6: 93.3% (28/30 ingestions)
  - Based on post-hoc analysis of IEM detection by component:
    - The Otsuka cloud server recorded 78.3% (94/120) of IEM ingestions.
    - The patches detected 98.3% (118/120) of IEM ingestions.
  - Results from this study indicate that there is a > 20% false negative rate with this device.
  - The mean (standard deviation) time from IEM detection by the patch to registration of the ingestion on the Otsuka cloud server was 21.4 (30.1) minutes. The design requirement for the Proteus (b) (4) application as cleared in K133263/S001 (page1102

of 1414) and K150494 required the wearable patch to upload any detected ingestion event within (b) (4) minutes. The system did not meet this performance requirement.

- 316-13-206b: OSMITTER 316-13-206B Substudy: A Substudy to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Period
  - This was an open-label, single-arm, single day study in 29 healthy volunteers.
  - The primary objective was to measure the accuracy of IEM detection using the placebo + IEM, and to evaluate the latency period between site-reported ingestion time and detection of the ingestion event by the Patch.
  - Secondary objectives were to measure the latency period between the Patch detection of the ingestion event and transmission of the event in the Otsuka Cloud-based Server.
  - This study used the (b) (4) version of the IEM; however, this trial only used placebo + IEM tablets.
  - Between 93.1 and 100% of ingestions were detected by the Patch.
  - The latency period (in minutes) from Patch detection (acquisition time) to the time of detection in the Otsuka cloud-based server (server time) had mean (SD) times of 7.5 (23.7), 10.3 (20.9), 6.2 (10.4), and 6.2 (8.9) at Hours 0, 2, 4, and 6, respectively. The range of the latency time at all scheduled time points was 0.4 to 123.2 minutes.
  - Overall detection accuracy improved in study 206b (as compared to 206a). Data latency also improved but still showed an extremely large distribution throughout time. It also did not include the time from tablet ingestion to IEM activation.

Note from the OPQ review: Both the 206A and 206B studies demonstrate that the Otsuka software (b) (4) has significant data latency that is not consistent with the IEM cleared under 510(k). Even under idealized study conditions a substantial fraction of patients will not receive positive detection confirmation before (b) (4) 30 minute (b) (4) This performance is <u>not adequate</u> to ensure safety and effectiveness for the intended use.

- 316-14-220: 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
  - This was an open-label trial in 37 patients with schizophrenia to evaluate the usability of the MIND1 System.
  - This trial included a screening period (≤ 2 weeks), a two-part treatment period (training period up to 3 weeks, independent phase approximately 5 weeks; 8 weeks total), and a safety follow-up period (2 weeks).
  - The primary objective of this study was to measure the usability of the MIND1 System by adult subjects with schizophrenia with regards to the ability to replace and pair the Patch independently and successfully by the end of the Week 8 trial visit.
  - Although safety data from this study were included in the application, efficacy data were not.

- The Applicant also submitted an unnumbered Human Factors (HF) validation study which was reviewed by Loretta Holmes, BSN, PharmD, in the Division of Medication Error Prevention and Analysis (DMEPA). This is considered the "pivotal" study to support this application. Prior to submitting this application, the Agency and the Applicant agreed that a HF study would be required to demonstrate that the product could be used by the intended patient population and that would it perform as labeled.
    - This study included a total of 36 patients: 12 with schizophrenia, 14 with MDD, and 10 with bipolar disorder. All participants were required to own and use smartphones.
    - 17 subjects received training ("assisted onboarding") on use of the System prior to testing (5 schizophrenia, 7 MDD, 5 bipolar).
    - 19 subjects received no training (7 schizophrenia, 7 MDD, 5 bipolar) and were required to complete all onboarding steps independently.
    - Participants were asked to complete a set of tasks in a simulated test environment.
    - Moderators did not intervene at any point while participants were attempting tasks.
    - Critical tasks were defined as tasks that are required for safe and effective use of the product.
    - 35 of 36 patients encountered difficulties or experienced errors performing at least one critical task; most patients experienced difficulties or errors on multiple critical tasks (total of 29 difficulties and 88 failures). In other words, only one subject was able to successfully complete all tasks *required* for safe and effective use of the product. Despite this, the Applicant concluded that these results demonstrated that patients can use the interface safely and effectively. This conclusion seems wholly unfounded in the face of the data provided.
    - DMEPA noted that the large number of failures and difficulties seen in this study is a departure from similarly designed studies with other products seen by the Agency. In a small sample size, a finding of this magnitude is especially concerning since this serves as an indicator for performance expected in actual use.
    - The inability for patients to correctly use the app and other components of the system, including the patch, (b) (4) This could also result in dosing errors which, in turn, could result in symptom relapse (if missed dose) or adverse events (if extra dose taken).

8. Safety

The overall assessment of safety for aripiprazole remains unchanged as a result of these studies. In general, adverse events were consistent with the know safety profile of aripiprazole or were dermal adverse events related to the Patch. One special safety study to evaluate skin irritation was submitted with this application:

- 316-13-205: 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
    - This was an open-label, randomized, controlled, 28-day study in which 30 healthy subjects were recruited (23 completers) to evaluate the skin irritation potential and overall safety and tolerability of the RP4 patch when applied to normal skin.

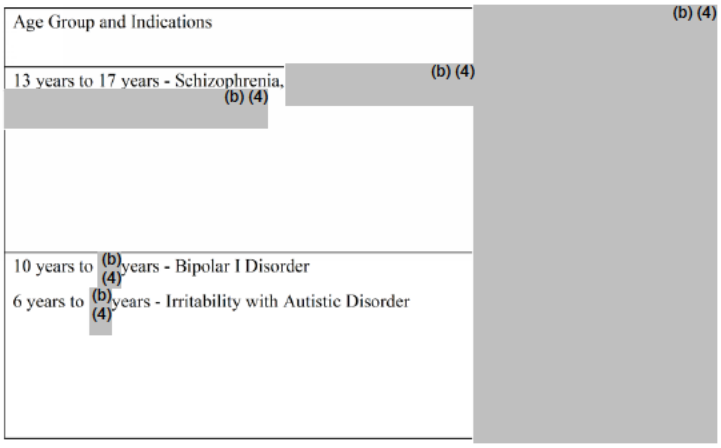
- Secondary endpoints for this trial were to evaluate the adhesiveness of the RP4 Patch and the potential for skin irritation of the RP4 Patch versus a control (2 x 2 cm pad attached to a nonporous plastic film adhesive bandage) when applied to normal skin.
- Skin irritation scores were determined for the RP4 Patch and control sites before application on Day 1, and after removal on Days 8, 15, 22 and 29. Adhesion scores were collected after the RP4 Patch and control were applied on Day 1, and before they were removed on Days 8, 15, 22 and 29. In addition, patients recorded in a diary when the RP4 Patch became loose or fell off. Adhesiveness was scored by trial site personnel using the information in the diary and/or visualization of the RP4 Patch and control at each of the 5 visits. A visual analog scale (VAS) for pruritus evaluation was administered at each site visit.
- The RP4 and control patches had similar performance in terms of adhesion, erythema, edema, and pruritus. Most patients experienced between 50 and 75% lift off of the patches. This study appears to indicate that the RP4 Patch can cause skin irritation and that adhesion may not be optimal; however, because these results are similar to the control patch, the electronic components within the RP4 Patch do not appear to worsen irritation or adhesion beyond what can be expected from the control.

9. Advisory Committee Meeting

No Advisory Committee meeting was held. The application was discussed internally at an Office of New Drugs (OND) Regulatory Briefing on February 26, 2016. The concerns raised by OPQ and DMEPA were presented and the Division discussed the preliminary recommendation to issue a Complete Response; OND leadership agreed with the Division's plan.

10. Pediatrics

The Applicant has an agreed Pediatric Study Plan (June 11, 2014). They intend to defer pediatric studies as follows:



11. Other Relevant Regulatory Issues

The OPQ facilities review team did not recommend approval as the drug substance manufacturer (Otsuka, Saga, Japan) has a "withhold" recommendation after a recent surveillance inspection.

12. Labeling

Based on the HF study, this product cannot be used as proposed in the Applicant's draft labeling. The deficiencies in this application preclude a more detailed review of labeling.

13. Recommendations/Risk Benefit Assessment

The Applicant has failed to demonstrate that this product can be used safely and effectively for its proposed indication in the intended population.

The system itself fails to meet the performance requirements (b) (4) This performance is not adequate to ensure safety and effectiveness for the intended use.

In addition to these system deficits, patients are not able to use the system as intended. Although an early study suggested patients felt the app was easy to use, more rigorous data collection in a formal HF study identified difficulties and errors in a number of critical tasks; adequate performance on these tasks is required for safe and effective use of the product. Only one of the 36 patients in the HF study was able to successfully use the product as intended.

Finally, the OPQ facilities review team did not recommend approval given that the drug substance manufacturer (Otsuka, Saga, Japan) has a "withhold" recommendation after a recent surveillance inspection.

In light of these deficiencies, I recommend a Complete Response action.

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/s/

TIFFANY R FARCHIONE
04/26/2016

MITCHELL V Mathis
04/26/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207202
Priority or Standard	Standard
Submit Date(s)	26 June 2015
Received Date(s)	26 June 2015
PDUFA Goal Date	26 April 2016
Division/Office	Division of Psychiatry Products/ ODE1
Reviewer Name(s)	ANDREASON, Paul J
Review Completion Date	3 March 2016
Established Name	Aripiprazole + IEM (OPC-14597 Digital, MIND1)
(Proposed) Trade Name	Abilify-MyCite®
Applicant	Otsuka Pharmaceutical Development and Commercialization, Inc.
Formulation(s)	Oral Tablet 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg
Dosing Regimen	Variable based on indication
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Complete Response/ Not approvable
Recommended Indication(s)/Population(s) (if applicable)	

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IEM	Ingestible Event Marker
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka or Applicant) apply for the approval of aripiprazole (Abilify) with the Ingestible Event Marker [IEM (OPC-14597 Digital)] under the trade name of Abilify-MyCite. Abilify-MyCite is a tablet consisting of a combination product of an approved drug product (Abilify) and medical device [IEM (OPC-14597 Digital)], and in the proposed combination, the indications are unchanged in either intended use or formulation apart from the inclusion of the IEM (b) (4) within the tablet. These indications include the treatment of Schizophrenia, Bipolar Disorder Type 1, or adjunctive treatment for Major Depressive Disorder. Specific sections of the Chemistry, Manufacturing, and Controls (CMC) information for this NDA e.g. drug substance and IEM, can be cross-referenced in its entirety to NDA 21- 436 and 510(k) K113070, K131009, and K133263, its amendments and annual report updates.

This NDA includes CMC information pertaining to the proposed combination product, aripiprazole + IEM tablets. Abilify tablets are commercially available in six strengths of 2-, 5-, 10-, 15-, 20- and 30- mg (Abilify family) and consequently the proposed combination products have been developed in the same six strengths by embedding an IEM into aripiprazole tablet.
The development of this combination product focused on formulation development, tablet process development and stability assurance, and consumer usability.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant for Abilify-MyCite provide a product for review that is an advance in technology. (b) (4) Abilify-Maintena provides the same drug substance over a 4-week treatment period with 100% adherence (for that 4-week period) and direct health-care provider verification of the drug's administration.

In the pivotal Consumer Use Trial, 35/36 patients were not able to use Abilify-MyCite as it was labeled; therefore, the Applicant did not provide adequate evidence that Abilify-MyCite could be used as intended. The patient user interface remains suboptimal and does not support safe and effective use in the intended population.

The risks for medication errors have not been adequately addressed and no modifications to the system have been proposed by the Applicant. The critical task failures seen in the Consumer

Use study could result medication errors in real life setting (e.g., extra doses and missed doses).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Schizophrenia, Bipolar disorder, and Major Depressive Disorder (MDD) are serious and common mental disorders in the United States. Depressive disorders account for 40.5% of the disability caused by mental illness worldwide. In 2014, an estimated 15.7 million adults aged 18 or older in the United States had at least one major depressive episode in the past year. This number represented 6.7% of all U.S. adults. Single agent treatments of Major Depressive Disorders are often inadequate. Difficulty with treatment adherence is common in all three conditions. One study found that 25% of patients told their doctors they were taking their medication when, in fact, the pharmacy database showed that they were not. Alternatively, non-adherence may be passive as patients forget or do not understand the instructions, or are unable to perform the activity correctly. All three conditions require extended treatment with predictable and monitorable adherence to treatment.

Antipsychotic drug treatment is frequently used in all three conditions. It is widely accepted that parenterally administered depot antipsychotic drugs improve drug-treatment adherence. There are several long-acting antipsychotic drug products available. Of particular note is Abilify Maintena which contains the active drug substance in Abilify-MyCite. Long-acting parenteral antipsychotics, depending on the drug, may be administered as frequently as weekly and as infrequently as monthly. These drugs are administered during a clinic visit by a health-care provider; therefore, treatment adherence is monitored at a level that is very dependable.

The Applicant for Abilify-MyCite provides a product for review that is an advance in technology (b) (4) Abilify-Maintena provides the same drug substance over a 4-week treatment period with 100% adherence (for that 4-week period) and direct health-care provider verification of the drug's administration. In the pivotal Consumer Use Trial, 35/36 patients were not able to use Abilify-MyCite as it was labeled; therefore, the Applicant did not provide adequate evidence that Abilify-MyCite could be used as intended.

The patient user interface remains suboptimal and does not support safe and effective use in the intended population. The risks for medication errors have not been adequately addressed and no modifications to the system have been proposed by the Applicant. The critical task failures seen in the Consumer Use study could result medication errors in real life setting (e.g., extra doses and missed doses).

Given the number of critical task failures spread across all user groups, it is not apparent that training or labeling the product for a certain user

population in actual use would be an option. The Abilify-MyCite user interface must be modified to achieve reasonable success of use as labeled. I do not recommend approval at this point until the Abilify-MyCite user interface is modified to the point it achieves reasonable success of use as labeled.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Schizophrenia is a serious chronic disorder which affects how a person thinks, feels and acts. Someone with schizophrenia may have difficulty distinguishing between what is real and what is imaginary; may be unresponsive or withdrawn; and may have difficulty expressing normal emotions in social situations. Schizophrenia is also associated with a decline in cognitive as well as social functioning. The cause of schizophrenia is still unclear. Some theories about the cause of this disease include: genetics, metabolic neuropathology, and/or possible viral infections and immune disorders. Schizophrenia affects about 1% of the world population. In the United States one in a hundred people, about 2.5 million, have this disease. It knows no racial, cultural or economic boundaries. Symptoms usually appear between the ages of 13 and 25, but often appear earlier in males than females. Schizophrenia requires chronic treatment with a goal to prevent acute relapses. The prevention of acute relapses correlates with a slower progression of cognitive and social decline. Chronic treatment includes the chronic administration of some form of antipsychotic drug. Adherence to medical treatment for patients with schizophrenia is identified as a core treatment problem which, if improved, will improve the patients' outcome. (Source- http://www.mentalhealthamerica.net/conditions/schizophrenia). Bipolar disorder, prior to DSM-III and still known colloquially as manic-depressive illness, is a serious medical illness that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. More than 5.7 million American adults or 2.6 percent of the population age 18 or older in	**Products that improve adherence to effective treatments will improve patient outcomes.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	any given year have bipolar disorder. Bipolar disorder often develops in a person's late teens or early adult years. At least half of all cases start before age 25. Some people have their first symptoms during childhood, while others may develop symptoms late in life. People often live with the disorder without having it properly diagnosed and treated. Symptoms of bipolar disorder can be severe. These are different from the normal ups and downs that everyone goes through from time to time. Bipolar disorder symptoms can result in damaged relationships, poor job or school performance, and even suicide, violence and incarceration. Bipolar disorder can be treated, and people with this illness can lead full and productive lives. Scientists continue to study the possible causes of bipolar disorder. Most scientists agree that there is no single cause. Rather, many factors likely act together to produce the illness or increase the risk of developing this disorder. Lack of adherence to medical treatment is associated with an increased risk of relapse to either a depressive or manic phase of the illness. (Source https://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml; https://bbrfoundation.org/frequently-asked-questions-about-bipolar-disorder?gclid=CjwKEAiAo7C2BRDgqODGq5r38DsSJAAv7dTPYdyN6XOFCgfEKFfM83e0UURMlUKyFTqqbq-sS3GgRBoCVr_w_wcB). Major Depressive Disorder (MDD) is one of the most common mental disorders in the United States. MDD is defined as an episode of depressed mood or loss of interest or pleasure which caused significant distress or disability, nearly every day for at least 2 weeks without a history of mania or hypomania, an explanatory medical condition, or substance use disorder. It is characterized by discrete episodes of at least 2 weeks' duration (although most episodes last considerably longer) involving clear-cut changes in affect, cognition, and cognitive and motor slowing and inter-episodic remissions. A diagnosis based on a single episode is possible, although the disorder is a recurrent one in the majority of cases. Careful consideration is given to the delineation of normal sadness and grief from a major depressive episode. Depressive disorders account for 40.5% of the disability caused by mental illness worldwide. In 2014, an	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	estimated 15.7 million adults aged 18 or older in the United States had at least one major depressive episode in the past year. This number represented 6.7% of all U.S. adults. Single agent treatments of Major Depressive Disorders are often inadequate. Difficulty with treatment adherence is common. One study found that 25% of patients told their doctors they were taking their medication when, in fact, the pharmacy database showed that they were not. Alternatively, non-adherence may be passive as patients forget or do not understand the instructions, or are unable to perform the activity correctly.	
Current Treatment Options	It is widely accepted that parenterally administered depot antipsychotic drugs improve drug-treatment adherence. There are several long-acting antipsychotic drug products available. Of particular note is Abilify Maintena which contains the active drug substance in Abilify-MyCite. These drugs may be administered as frequently as weekly (Prolixin decanoate) and as infrequently as monthly (haloperidol-decanoate, Zyprexa-Relprev, Risperdal-Consta; Invega-Sustenna; Abilify Maintena). These drugs are administered during a clinic visit by a health-care provider; therefore, treatment adherence is monitored at a level that is very dependable. Zyprexa-Relprevv is approved for the treatment of schizophrenia (b) (4) . Risperdal Consta is approved for the maintenance treatment of Bipolar Disorder and the treatment of Schizophrenia. Invega Sustenna is approved for the treatment of Schizophrenia and Schizoaffective Disorder.	
Benefit	The Applicant for Abilify-MyCite provide a product for review that is an advance in technology. (b) (4) . Likewise, Abilify-Maintena provides the same drug substance over a 4-week treatment period with 100% adherence (for that 4-week period) and direct health-care provider verification of the drug's administration. 35/36 patients were not able to use Abilify-MyCite as it was labeled.	(b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• 35/36 patients were not able to use Abilify-MyCite as it was labeled. • The patient user interface remains suboptimal and does not support safe and effective use in the intended population • The risks for medication errors have not been adequately addressed and no modifications to the system have been proposed by the Applicant	The critical task failures seen in the HF study could result medication errors in real life setting (e.g., extra doses and missed doses)
Risk Management	• Given the number of critical task failures spread across all user groups, it is not apparent that training or labeling the product for a certain user population in actual use would be an option.	The Abilify-MyCite user interface must be modified to achieve reasonable success of use as labeled.

2 Therapeutic Context

2.1. Analysis of Condition

Schizophrenia is a serious chronic disorder which affects how a person thinks, feels and acts. Someone with schizophrenia may have difficulty distinguishing between what is real and what is imaginary; may be unresponsive or withdrawn; and may have difficulty expressing normal emotions in social situations. Schizophrenia is also associated with a decline in cognitive as well as social functioning. The cause of schizophrenia is still unclear. Some theories about the cause of this disease include: genetics, metabolic neuropathology, and/or possible viral infections and immune disorders. Schizophrenia affects about 1% of the world population. In the United States one in a hundred people, about 2.5 million, have this disease. It knows no racial, cultural or economic boundaries. Symptoms usually appear between the ages of 13 and 25, but often appear earlier in males than females. Schizophrenia requires chronic treatment with a goal to prevent acute relapses. The prevention of acute relapses correlates with a slower progression of cognitive and social decline. Chronic treatment includes the chronic administration of some form of antipsychotic drug. Adherence to medical treatment for patients with schizophrenia is identified as a core treatment problem which, if improved, will improve the patients' outcome. (Source- http://www.mentalhealthamerica.net/conditions/schizophrenia).

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Single agent treatments of Major Depressive Disorders are often inadequate. Difficulty with treatment adherence is common. One study found that 25% of patients told their doctors they were taking their medication when, in fact, the pharmacy database showed that they were not. Alternatively, non-adherence may be passive as patients forget or do not understand the instructions, or are unable to perform the activity correctly.

(Source: http://www.mentalhealth.com/home/dx/majordepressive.html; http://dsm.psychiatryonline.org/doi/full/10.1176/appi.books.9780890425596.dsm04; http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml ; http://www.psychiatrictimes.com/articles/adherence-treatment-regimens-major-depression-perspectives-problems-and-progress)

2.2. Analysis of Current Treatment Options

There are many approved drug products for the treatment of schizophrenia, MDD, and Bipolar Disorder; (b) (4) Abilify is also available as a long acting parental depot formulation (Abilify-Maintena) that is effective for 4-weeks' duration and is administered by health-care providers during a clinic visit.

Adherence to drug treatment for Schizophrenia, Bipolar Disorder and MDD is crucial to prevent relapse of the core symptoms of these disorders. It is widely accepted that parenterally administered depot antipsychotic drugs improve drug-treatment adherence. These drugs may

be administered as frequently as weekly (Prolixin decanoate) and as infrequently as monthly (haloperidol-decanoate, Zyprexa-Relprev, Risperdal-Consta; Invega-Sustenna; Abilify Maintena). These drugs are administered during a clinic visit by a health-care provider; therefore, treatment adherence is monitored at a level that is very dependable.

In summary, there are several long-acting antipsychotic drug products available. It is widely accepted that depot formulations of antipsychotic drug products improve treatment adherence. Of particular note is Abilify Maintena which contains the active drug substance in Abilify-MyCite. Zyprexa-Relprevv is approved for the treatment of schizophrenia. (b) (4) . Risperdal Consta is approved for the maintenance treatment of Bipolar Disorder and the treatment of Schizophrenia. Invega Sustenna is approved for the treatment of Schizophrenia and Schizoaffective Disorder.

The Applicant for Abilify-MyCite provide a product for review that is an advance in technology but not yet in treatment efficacy. (b) (4) Likewise, Abilify-Maintena provides the same drug substance over a 4-week treatment period with 100% adherence (for that 4-week period) and direct health-care provider verification of the drug's administration.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Abilify-MyCite is not yet marketed anywhere in the world. This is a combination product that contains the oral formulation of Abilify and the Proteus Ingestible Event Marker [IEM (OPC-14597 Digital, MIND1)]. The IEM (OPC-14597 Digital, MIND1) is not combined with any other drug substance or product at this time nor is it marketed independently as a therapeutic device. Abilify (aripiprazole) is currently marketed in several formulations including generic drug products.

The aripiprazole oral tablet was first approved for the treatment of schizophrenia in Nov 2002 in the United States (US) NDA (NDA 21-436). It is also approved for the acute treatment of manic or mixed episodes associated with bipolar I disorder (as monotherapy and as an adjunct to lithium or valproate), for the maintenance treatment of bipolar I disorder (both as monotherapy and as an adjunct to lithium or valproate), and for adjunctive treatment of MDD. The pediatric oral tablet approved indications for agitation associated with autistic disorder and Tourette's disorder and oral solution, orally disintegrating tablets, and intramuscular injectable formulations and associated indications are outside the scope of the Abilify-MyCite drug-device combination. Abilify- Maintena (aripiprazole long acting intramuscular depot formulation) was

approved for the treatment of schizophrenia on 1 March 2013.

3.2. Summary of Pre-submission/Submission Regulatory Activity

The regulatory history for Abilify-MyCite follows the history off the two component companies and their cooperation to produce Abilify-MyCite.

The company Proteus Digital Health, Inc. submitted and received 510(k) clearance in February 2014 for a device called the Proteus Patch Including Ingestible Sensor. Proteus is a device that consists of an ingestible electronic sensor, a wearable patch with embedded software, and a mobile app. The Proteus Patch is a body-worn electronic sensor that collects physiological and behavioral metrics such as heart rate, activity, body angle relative to gravity, and time-stamped user-logged events generated by swallowing the ingestible sensor. The sensor is embedded inside a tablet for ease of swallowing. Once the ingestible sensor reaches the stomach, it activates and communicates its presence and unique identifier to the patch. The patch stores and wirelessly (via Bluetooth) sends the physiological, behavioral, event, and ingestion data to a smartphone containing the mobile app.

(b) (4)

Such a product is considered a drug/device combination product assigned to CDER as the lead center. Currently, FDA has (b) (4) OTSUKA IND 115927 for Abilify (aripiprazole) IEM for schizophrenia (Recent DAARTS Applicant communications, 2/10/14 meeting minutes; 6/11/14 (pediatric plan).

The following sections highlight regulatory interactions with CDER and CDRH.

(b) (4)

(b) (4)

- In June 2014 CDER –IO held a teleconference with Proteus representative and provided a follow-up e-mail to indicate that the combination product regulatory pathway would be an NDA and recommended that the supportive data for the device should be submitted in a device master file. Subsequent communications confirmed that the combination product included the software.
- CDER issued a letter/email in to Osuka in August, 2014 confirming that the combination product reviewed under NDA should be the entire system consisting of the drug, the IEM, the patch, and the mobile app software. At the same time Otsuka was interacting with CDER-IO, they also contacted CDRH Center Director Dr. Shuren for assistance in resolving this same issue.
- (b) (4)
- The Applicant met with FDA in a pre-filing meeting on 5 May 2015. Based on the functionality of the combined product, (b) (4) . The Applicant received concurrence from the FDA that the Human Factors Validation study provided sufficient support on face for the claim that the NDA may be filed. This NDA is therefore filed on the basis of one completed Human Factors Validation study that included 36 patients from three different diagnostic groups (schizophrenia, major depressive disorder, bipolar 1 disorder) and who were divided between two conditions of use (assisted and unassisted). FDA agreed that an integrated summary of efficacy or safety since the efficacy and safety of the components have already been demonstrated and the indications for Abilify-MyCite are the same as those for the Abilify oral tablet in adults.
- The NDA was submitted to the FDA on 26 June 2015.

3.3. Foreign Regulatory Actions and Marketing History

Abilify-MyCite is not marketed anywhere in the world.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

There are no OSI concerns at the writing of this review. There is one pivotal human factors trial to test if the product may be used as labeled. 35/36 patients failed one or more critical steps in using the product. The integrity of this data is not in question.

4.2. Product Quality

CMC and CDRH are concerned that the Applicants have not demonstrated that the IEM device in combination with Abilify still performs within acceptable specifications. There is no in vivo testing of the (b) (4) IEM + Aripiprazole. The Applicant's justification of the (b) (4) IEM's in vivo performance based on in vitro testing; however, the in vitro testing environment (pH = 7.4) is not representative of the gastric environment (pH=2-4).

CMC and CDRH note that the chip-to-skin-patch-transmission performance rates for the (b) (4) prototype when associated with Abilify are below the historical success rate for the (b) (4) model with placebo; therefore, when (b) (4) is associated with placebo and the chip-to-skin-patch-transmission performance rates improve, CDRH and CMC cannot be certain that Abilify does not affect the performance of the chip-to-skin-patch-transmission.

4.3. Clinical Microbiology

There were no clinical microbiology data to review

4.4. Nonclinical Pharmacology/Toxicology

There were no non-clinical data to review.

4.5. Clinical Pharmacology

There were no new Clinical Pharmacology data for Abilify to review.

4.6. Devices and Companion Diagnostic Issues

CDRH has the following concerns that affect this products approvability:

- In vivo testing of Aripiprazole + IEM did not use the model of ingestible sensor proposed for the marketed combination product. The testing also indicates poor data transmission and/or compatibility problems (b) (4) CDRH recommends, at a minimum, software fixes and re-validation of the entire system to include in vivo testing of Aripiprazole + (b) (4)) IEM.
- The Type V drug master file submitted for the Proteus IEM contains very little information on the *current* ingestible sensor design and relies heavily on references to previous 510(k) clearances. We recommend that Proteus resubmit or substantially amend the file to contain relevant information (b) (4) .
- (b) (4)
  Given the reliance on electronic only labeling, unclear DMF information, and poor data transmission performance, CDRH does not believe that this is appropriate within the NDA paradigm.

4.7. Consumer Study Reviews

The one pivotal trial in this NDA is a Consumer Usability Study. The Applicant for Abilify-MyCite provide a product for review that is an advance in technology (b) (4) . The efficacy of the drug substance, Abilify immediate release formulation, is not expected to be affected by the inclusion of the (b) (4) IEM into the tablet; therefore, the efficacy of the drug substance is presumed to be the same for regulatory purposes.

(b) (4)

The Applicant was required to perform one consumer usability study that demonstrated that

trained or untrained correct use of the product was likely possible. The review of this study was performed by the Division of Medication Error Prevention and Analysis (DMEPA). The following is a summary of that review.

The study design followed a human factors validation protocol in which participants were asked to complete a set of tasks in a simulated test environment, created to match the real-world setting of participants. Recruited based on a diagnosis of Major Depressive Disorder (MDD), Bipolar 1 Disorder (BP1) and Schizophrenia (SCZ), along with ownership and frequency of smartphone use, participants were provided with the materials comparable to those that would be available to them in real-world use. Moderators did not intervene at any point while participants were attempting tasks (Source NDA 207-202 Section 1.11.1 Human Factors Summary Report).

Objective
Demonstrate that intended users can use the system safely and effectively for its intended purpose

Study Participants (36)

Untrained Arm (19)
- Schizophrenia (7)
- Major Depressive Disorder (7)
- Bipolar Disorder (5)

Trained* Arm (17)
- Schizophrenia (5)
- Major Depressive Disorder (7)
- Bipolar Disorder (5)

*Trained HCPs assisted this group on Day 1

Method
All participants experienced comparable simulated use environments. The study sessions were conducted at market research facilities representing the environment of expected reasonable use and included a well-lit room with a table upon which the participant interacted with the integrated kit components to enact the use scenarios. As the Abilify-MyCite System will be utilized by the intended users at their own discretion, the study did not include simulated environmental distractions. However, no specific effort was made to control distractions that may occur naturally during testing (e.g., ambient noise, participant's cell phone ringing).

The Abilify-MyCite app on the iPhone was controlled by a computer simulator, which was used

to populate particular notifications and functions on the app that would be seen in actual use. The simulator was run by a dedicated operator trained on simulator use. The operator was a qualified researcher, with in-depth knowledge about the study as well as specifics of the test procedure.

During the study, the participants are asked to simulate use of the product, by going through the steps required for its use. I will refer to these steps as "tasks" throughout this discussion. The simulation is done with a placebo tablet placed in water and with the participant wearing a body sleeve upon which they affix the patch. As the participants simulate the use of the system, the investigators observe their performance of those steps or ask the participant questions about them to determine if they have difficulty with the step or whether they fail to perform the step.

Not all tasks are treated equally in HF testing. The tasks are categorized as "necessary" or "critical" and this categorization becomes important when DMEPA interpret the results of the study. Necessary tasks are those that are required in order to use the product at all, for example downloading the app onto the phone. Critical tasks, on the other hand, are those that if done incorrectly, could result in medication errors and impact whether the system is being used safely. While DMEPA looked at all the errors in the study carefully, they focus on those errors with critical tasks, since they carry greater risks to the patient.

Results for Critical Tasks

- 35 out of 36 had use difficulty or task failures(s) (~97%)
    - 19/19 Untrained
    - 16/17 Trained

- Total use difficulties (n=29), Total task failures (n=88)
    - Untrained participants: Difficulties (n=16), Failures (n=58)
    - Trained participants: Difficulties (n=13), Failures (n=30)

Summary & Conclusion of DMEPA Review

- The inability for patients to use the system would likely not allow for accurate measurement of medication adherence
- The critical task failures seen in the HF study could result medication errors in real life setting (e.g., extra doses and missed doses)
- Given the number of critical task failures spread across all user groups, it is not apparent that training or labeling the product for a certain user population in actual use would be an option. The risks for medication errors have not been adequately addressed and no modifications to the system have been proposed by the Applicant. The patient user interface remains suboptimal and does not support safe and effective use in the

intended population

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Several studies were performed involving human subjects (patients and healthy volunteers) during the development of Abilify-MyCite. The design of the studies varied. They examined the performance of the (b) (4) IEM embedded in placebo when administered to healthy normal volunteers (HNV), the performance of the combination of Abilify with an (b) (4) IEM in patients who were taking Abilify therapeutically, and studies of whether or not patients could follow the directions without actually ingesting any test product. None of these studies gathered data on comparative efficacy. Therefore the goal of the clinical review was to examine the study results for adverse events that would not have been expected from Abilify alone.

The following is a table of the clinical studies in this development program.

Type of Trial (Trial Phase)	Protocol Number, Title, Location of Trial	Primary Trial Objective(s)	Trial Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled/ Treated/ Completed	Healthy Subjects or Diagnosis of Subjects	Treatment Duration
Exploratory, Safety (Phase 4)	316-13-204 A Formative Usability Study of the Otsuka MIND1 Prototype by Subjects with Bipolar Disorder or Major Depressive Disorder United States	To obtain feedback from subject and caregiver (if applicable) about the use of the MIND1 System and any application (ie, software) updates that were made during the trial.	Open-label, single-arm	MIND1 System; oral ingestion of placebo + IEM with prescribed medication; Patch application to skin with IEM ingestion.	58/58/47	Subjects with bipolar disorder or MDD	16 weeks
Exploratory, Safety (Phase 1)	316-13-205 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 United States	To evaluate skin irritation potential and overall safety and tolerability for the RP4 Patch when applied to normal skin.	Open-label, controlled, randomized	The RP4 Patch and control were applied on Days 1, 8, 15, and 22 for a total of 4 applications over a consecutive 28-day period.	30/30/23	Healthy subjects	28 days
Exploratory, Safety (Phase 4)	316-13-206a OSMITTER 316-13-206A: A Substudy to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information	To measure the accuracy of IEM detection by the MIND1 System (Otsuka app) using both aripiprazole + IEM tablets and the placebo + IEM tablets, and to evaluate the latency period	Open-label, single-arm	Following placement of the Patch by clinic staff, subjects ingested one IEM tablet (aripiprazole or placebo) approximately every 2 hours, for a total of 4 ingestions	30/30/30	Healthy subjects	1 day

	Device #1 (MIND1) System and Determine the Latency Period United States	between ingestion and detection for both ingestions.					
Exploratory, Efficacy, Safety (Phase 4)	316-13-206b OSMITTER 316-13-206B Substudy: A Substudy to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Period United States	To measure the accuracy of IEM detection by the MIND1 System using the placebo tablet + IEM tablet, and to evaluate the latency period between site- reported ingestion time and detection of the ingestion event by the Patch.	Open-label, single-arm	During Visit 1 (Day 1), subjects ingested 1 placebo tablet + IEM approximately every other hour, for a total of 4 ingestions (Hour 0, 2, 4, and 6).	29/29/29	Healthy subjects	1 day
Therapeutic exploratory, Safety (Phase 2a)	316-14-220 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 United States	To measure the usability of the MIND1 System by adult patients with schizophrenia with regards to the ability to replace and pair the Patch independently and successfully by the end of the Week 8 trial visit.	Open-label, single-arm	The drug-device combination consisted of a tablet of aripiprazole (10, 15, 20, or 30 mg) plus the embedded IEM. All patients took aripiprazole + IEM tablets during the treatment period of this trial.	37/37/27 (Cohort 1 as of 24 Dec 2014 cutoff date) There are 2 subject cohorts	Subjects with schizophrenia	8 weeks

CSR = clinical study report; IEM = ingestible event marker; MDD = major depressive disorder; MIND1 = Medical Information Device 1

5.2. **Review Strategy**

The Clinical Review of this NDA serves a coordinating function more than a review function.

This is because the NDA contains no new clinical trials data; nonetheless, the product has psychiatric indications and therefore fell under the jurisdiction of the Division of Psychiatry Products to provide the primary clinical review. The Abilify-MyCite product is a combination of a device for which no comparative clinical data is available and a well-known immediate release formulation of aripiprazole, Abilify. The safety and efficacy profile of Abilify is established in previous NDA's to which the Applicant refers. The inclusion of the IEM device is not expected to alter the chemical properties or the therapeutic action of the drug substance. There is some question as to whether the performance of the IEM will be altered by its encasement in Abilify as opposed to placebo. This aripiprazole encasement performance of the (b) (4) IEM has not been established to the satisfaction of CDRH at the writing of this review. The single pivotal Consumer Usability study failed to demonstrate that the intended populations could use the drug product as it was labeled.

Since the safety and efficacy profile of the drug substance was not in question and there were no controlled clinical trials required for this development program, the Applicant was likewise not required to submit an integrated summary of efficacy or safety.

The Clinical Review strategy is therefore to review the individual open-label studies for unexpected adverse events.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Protocol No. 316-13-204 A Formative Usability Study of the Otsuka MIND1 Prototype by Subjects with Bipolar Disorder or Major Depressive Disorder

6.1.1. Study Design

Overview and Objective

Protocol No. 316-13-204 A Formative Usability Study of the Otsuka MIND1 Prototype by Subjects with Bipolar Disorder or Major Depressive Disorder

Objectives:

- Primary: To obtain feedback from subject and caregiver (if applicable) about the use of the MIND1 System and any application (ie, software) updates that are made during the trial.
- Secondary: To characterize the safety of the MIND1 System.
- Tertiary: To summarize the subject cohort's medication-taking adherence based on ingestible event marker (IEM) detections reported by the MIND1 System and to summarize adhesive and other user behaviors for the patch.

Trial Design

Trial 316-13-204 was an exploratory, open-label, single-arm, observational trial designed to evaluate the usability of the MIND1 System software, the safety of the MIND1 System, (b) (4) Following a 2-week screening phase, patients and their caregivers (if applicable) were to be given MIND1 System kits for use during the trial. The kits included placebo + IEM tablets, patches, a mobile computing device (e.g., smartphone) that included a short introductory video and the software applications (the Otsuka app (b) (4) and a printed reference guide. There was no active Abilify in this study.
Diagnosis and Main Criteria for Inclusion: Subjects were male or female, 18 years of age or older, with a current diagnosis of bipolar disorder or MDD, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, who were deemed stable by the clinical investigator (e.g., symptoms and medication) for a period of 3 months.

Number of Subjects:
Planned: 45 patients were planned to be enrolled in 2 cohorts, which were to have consisted of 30 patients with bipolar disorder and 15 patients with major depressive disorder (MDD), who were in the stable phase of their disease. Up to 10 additional patients in each cohort, in accordance with predetermined selection criteria, may have been enrolled in each cohort. At least one-half of patients with bipolar disorder or MDD may have designated a caregiver, if applicable, who supported or assisted the subject with their health and wellness.
Enrolled: 58 patients were enrolled and included in the Safety Sample.
Analyzed: 55 patients were included in the Efficacy Sample.

Duration of Treatment: The duration of this trial for each subject was approximately 20 weeks; 16 weeks were allotted for active subject participation using the MIND1 System, plus a 4-week safety follow-up (phone call) period.

Trial Assessments:
Usability: Usability evaluation was assessed using feedback from subject and caregiver questionnaires on the use of the MIND1 System.

Safety: Safety was assessed by AE reporting related to the MIND1 System. Pregnancy tests, vital signs measurements, and physical assessments were also conducted.

Adherence: Adherence was assessed by measuring the number of IEM detections and summarizing subject patch use.

Other: Observational assessments included the Clinical Global Impression - Severity Scale (CGI-S) and the Clinical Global Impression - Improvement Scale (CGI-I).

Screening: Screening evaluations include urine pregnancy tests, wireless coverage verification, review of subject selection criteria, medical history, psychiatric history, vital signs measurements, caregiver designation (if applicable), and CGI-S assessment.

Study Endpoints

Trial Assessments:

Usability: Usability evaluation was assessed using feedback from subject and caregiver questionnaires on the use of the MIND1 System.

Safety: Safety was assessed by AE reporting related to the MIND1 System. Pregnancy tests, vital signs measurements, and physical assessments were also conducted.

Adherence: Adherence was assessed by measuring the number of IEM detections and summarizing subject patch use.

Other: Observational assessments included the Clinical Global Impression - Severity

Scale (CGI-S) and the Clinical Global Impression - Improvement Scale (CGI-I).

Screening: Screening evaluations include urine pregnancy tests, wireless coverage verification, review of subject selection criteria, medical history, psychiatric history, vital signs measurements, caregiver designation (if applicable), and CGI-S assessment.

Criteria for Evaluation:

Primary Endpoint (Usability): The primary usability endpoint was to provide descriptive feedback on the usability of the mobile and web application (i.e., Otsuka app) to include mood, rest, activity, ingestion, and other related features of the MIND1 System.

Secondary Endpoint (Safety): The safety endpoints were the MIND1 System safety profile, defined as the number and nature of the device-related AEs, number of serious adverse events (SAEs), and number of unanticipated adverse device effects (ADEs) reported during the trial.

(b) (4)

Statistical Analysis Plan

This was an open-label study; therefore, statistical comparisons were not planned or performed.

Criteria for Evaluation:

Primary Endpoint (Usability): The primary usability endpoint was to provide descriptive feedback on the usability of the mobile and web application (i.e., Otsuka app) to include mood, rest, activity, ingestion, and other related features of the MIND1 System.

Secondary Endpoint (Safety): The safety endpoints were the MIND1 System safety profile, defined as the number and nature of the device-related AEs, number of serious adverse events (SAEs), and number of unanticipated adverse device effects (ADEs) reported during the trial.

(b) (4)

6.1.2. Study Results

Compliance with Good Clinical Practices

Disposition, Demographics, and Baseline Characteristics: Sixty-four patients were screened and 58 patients were enrolled in the trial, which included 35 patients (60.3%) with bipolar disorder and 23 (39.7%) patients with major depressive disorder. Eleven (19.0%) patients were discontinued from the trial. Of the enrolled patients, the mean age was 46.4 years, 63.8% (37/58) of patients were female, and 77.6% (45/58) were white.

(Safety) Results:

There were no deaths during the study. Five SAEs were reported in 4 patients: bacteraemia, periorbital cellulitis, tooth abscess, hallucination, and major depression. None of the SAEs were considered to be related to the MIND1 System; the device use was in some cases interrupted but not withdrawn.

There were two dropouts that were related to adverse events. Subjects (b) (6) and (b) (6) withdrew at the event of skin site rash or erythema respectively. Five patients withdrew consent for unspecified reasons, two were lost to follow-up, and two discontinued due to protocol deviation (one enrolled in another trial and one was dropped due to "non-compliance").

The following treatment-emergent adverse events were reported from at least 5% of patients: application site pruritus (6/58, 10.3%; all related to patch), application site erythema (5/58, 8.6%; all related to patch), application site rash (4/58, 6.9%; all related to patch), nausea (3/58, 5.2%), pruritus (3/58, 5.2%; all related to patch), and rash (3/58, 5.2%; one incidence related to patch).

Reviewer Conclusions: The skin related adverse events are consistent with previous experience with the MIND1 system. Nausea is difficult to assess as being device related as there is no comparator group. It seems highly unlikely that the serious adverse events are related to the MIND1 system as the device use though interrupted by events was not withdrawn and the continued use of the device did not result in a recurrence of the adverse event.

6.2. Protocol 316-13-205 A 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

6.2.1. Study Design

Overview and Objective

Protocol 316-13-205 A 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

Objectives:
Primary:

- To evaluate the potential for the RP4 Patch to cause skin irritation when applied to normal skin;
- To determine the overall safety and tolerability of the RP4 Patch when applied to normal skin.

Secondary:

- To evaluate the adhesiveness of the RP4 Patch when applied to normal skin;
- To evaluate the potential for the RP4 Patch versus a control to cause skin irritation when applied to normal skin.

Trial Design

Trial 316-13-205 was an open-label trial designed to evaluate the irritation potential of, and adhesion to, the skin of the RP4 Patch. This trial used a cumulative skin irritation Patch test to determine the total cumulative and mean skin irritation scores for the RP4 Patch and for the

control. The control was a 2 x 2 cm pad attached to a nonporous, plastic film adhesive bandage, which is commonly used in clinical research. The control was secured with hypoallergenic micropore tape, as needed.

After screening, patients were randomly assigned (1:1) to receive the RP4 Patch, which was applied on either the right or left side of the body, just above the lower edge of the rib cage; each subject received the control at the same location on their opposite side. The RP4 Patch and control were applied on Days 1, 8, 15, and 22 for a total of 4 applications over a consecutive 28-day period. Subsequent applications were to be at a slightly lower or upper position, as compared to the application site the prior week. After each application, the RP4 Patch and control were to remain in place until the next scheduled visit.

All patients received the RP4 Patch (Proteus Digital Health), which was applied to the skin, just above the lower edge of the rib cage (either the right or left side). The Patch was applied at the Day 1 visit, and then was to be worn by patients for 7 consecutive days until the next scheduled visit. The RP4 Patch was removed and reapplied at the Day 8, 15, and 22 visits and then was to be worn for 7 consecutive days after each of these applications; this produced a 28-day period of testing.

Trial Assessments: Skin irritation scores were determined for the RP4 Patch and control sites before application on Day 1, and after removal on Days 8, 15, 22 and 29. Adhesion scores were collected after the RP4 Patch and control were applied on Day 1, and before they were removed on Days 8, 15, 22 and 29. In addition, patients recorded in a diary when the RP4 Patch became loose or fell off. Adhesiveness was scored by trial site personnel using the information in the diary and/or visualization of the RP4 Patch and control at each of the 5 visits. A VAS for pruritus evaluation was administered at each site visit.

Safety assessments included collection and reporting of adverse events (AEs), both local and systemic, throughout the trial. Physical examinations, electrocardiograms (ECGs), vital signs, safety laboratory tests, and urinalyses were also conducted.

Primary Endpoint: The key primary endpoint was the change from baseline in total cumulative and mean skin irritation scores for each subject for the test product (RP4). The primary safety endpoint was the number and rate of AEs (topical and systemic) for each subject and for the test product, and any clinically relevant changes from baseline in physical examinations, vital signs, and clinical laboratory tests.

Secondary Endpoint: A secondary endpoint was the total and mean adhesion scores for the test product (RP4). The key secondary endpoint was the total cumulative and mean skin irritation scores for the test product (RP4) versus the control.

Study Endpoints

Skin irritation scores were determined using the Modified Draize method for the RP4 Patch and control sites before application on Day 1, and 30 minutes after removal on Days 8, 15, 22, and 29. Adhesion scores were collected after the RP4 Patch and control were applied on Day 1, and before they were removed on Days 8, 15, 22, and 29; a photo of the Patch and control placement was taken at each visit. In addition, patients recorded in a diary if or when the RP4 Patch or control became loose or fell off. Adhesiveness was scored by trial site personnel using the information in the diary and/or visualization of the Patch or control at each of the 4 visits. A visual analogue scale (VAS) for pruritus evaluation was administered at each site visit, and a photograph was taken in the event of any skin irritation.

6.2.2. Study Results

Patient Disposition

Subjects were healthy males and non-pregnant females who were 18 to 45 years of age. Forty-five patients were screened, and 30 patients were enrolled at 1 site in the US and treated in the trial. A total of 7 patients were discontinued from the trial. The majority of patients were female (21/30, 70%), and the majority of patients were white (27/30, 90.0%). The mean age of enrolled patients was 31.8 years (range 18 to 45 years).

Results

•Mild cumulative erythema was observed on Days 15, 22, and 29 for the control, and on Days 22 and 29 for the RP4 Patch.

•No edema (mean or cumulative), and very slight mean erythema and eschar formation were observed at all time-points for the RP4 Patch or control.

•Individual results for VAS suggest that several patients experienced an increase in pruritus over time, but median VAS scores (range: 1.0 to 10.0 mm) and change from baseline (range: 2.0 to 6.0 mm) were minimal across all time-points.

•Adhesion scores throughout the trial ranged from a mean of 2.3 to 2.8 for the control and 2.1 to 3.0 for the RP4 Patch, indicating that most patients experienced between 50% and 75% lift off of the patches.

•On Day 8, both the control and RP4 Patches completely detached for 68.0% (17/25) of patients.

•Adhesiveness scores generally improved over the course of the trial, but over 25.0% of patients had complete detachment of the control or RP4 Patch at each time-point.

On Day 29 of the trial, 47.8% (11/23) and 43.5% (10/23) of patients had complete detachment of the control or RP4 Patch, respectively.

•Generally, patients wore the RP4 patch for an average of 6 days with improvement in wearability of the RP4 patch over the course of the trial.

Safety

There were no deaths, or serious adverse events, or treatment related adverse events that lead to drop out associated with this study.

•In general, the RP4 Patch was well tolerated and caused little to no skin irritation.

•There were no reported AEs during the trial (systemic or topical).

•Three patients had potentially clinically relevant hematology values, and one subject had a potentially relevant chemistry value, all of which were not considered clinically relevant by the investigator.

•Individual results for skin irritation showed that 3 patients had mild erythema associated with the RP4 Patch, and 2 patients had mild erythema associated with the control, throughout the entire trial. Two patients had mild erythema associated with the RP4 Patch on Day 22, and one subject had mild erythema associated with the control on Day 15. One subject had mild erythema on Day 8 associated with both RP4 Patch and control. All instances of erythema were considered not clinically relevant by the investigator.

•Individual results for VAS suggest that several patients experienced an increase in pruritus over time, but median VAS scores (range: 1.0 to 10.0 mm) and change from baseline (range: 2.0 to 6.0 mm) were minimal across all time-points.

Reviewer Conclusion: This was a skin tolerance and adherence study of a small number of normal volunteers. There were no unexpected adverse events which would lead to changes in labeling or approval.

6.3. OSMITTER 316-13-206A: A Substudy to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Periodnsert Study Name

6.3.1. Study Design

Overview and Objective

OSMITTER 316-13-206A: A Substudy to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Period. The objectives of the study were to:
Primary: To measure the accuracy of ingestible event marker (IEM) detection by the MIND1 System using both aripiprazole-embedded IEM tablets and the placebo-embedded IEM tablets, and to evaluate the latency period between ingestion and detection for both ingestions.
Secondary: To evaluate the safety of the MIND1 System.

Trial Design

Approximately 32 healthy volunteer subjects were planned to be enrolled in this trial.

This trial was conducted to determine the accuracy of IEM detection by the MIND1 System by completing a series of patch applications and IEM ingestions in the clinic. Following placement of the patch by clinic staff, subjects ingested one IEM tablet approximately every 2 hours, for a total of 4 ingestions. The subjects ingested one 10-mg aripiprazole-embedded IEM (aripiprazole + IEM) tablet without food (Hour 0), one placebo-embedded IEM (placebo + IEM) tablet without food (approximately Hour 2), one placebo + IEM tablet with a high-fat meal (approximately Hour 4), and one placebo + IEM tablet without food (approximately Hour 6).

The clinic staff recorded the time of each IEM ingestion and the time it was detected by the software application on the MIND1 System smartphone. The duration of this trial for each subject was estimated to be 1 day of active participation plus a 2-week safety follow-up (phone call) period.

Trial Assessments: The assessment for the primary endpoint was the activation proportions of aripiprazole + IEM at Hour 0 and placebo + IEM, under each condition, at Hours 2, 4, and 6. The assessment for the secondary endpoint was the time from ingestion to detection of aripiprazole + IEM at Hour 0 and placebo + IEM, under each condition, at Hours 2, 4, and 6. Safety variables included adverse events (AEs), clinical laboratory tests, and vital signs.

6.3.2. **Study Results**

Thirty-eight subjects were screened and 30 subjects were enrolled in the trial. All 30 subjects completed the trial and were included in the ITT Sample and Safety Sample. The subject population was 56.7% female and 43.3% male; 53.3% White, 13.3% Asian, 10.0% Black or African American, 3.3% Native Hawaiian or other Pacific Islander, and 20.0% of another race; and 13.3% of Hispanic or Latino ethnicity and 86.7% not of Hispanic or Latino ethnicity. The mean age was 39.8 years and the mean body mass index was 25.5 kg/m2.

Technical Performance Results:
Accuracy:
•Clinic staff noted that the Otsuka app reported 76.7% (92/120) of IEM ingestions overall, and by hour:

- Hour 0: 73.3% (22/30 ingestions)
- Hour 2: 63.3% (19/30 ingestions)
- Hour 4: 76.7% (23/30 ingestions)
- Hour 6: 93.3% (28/30 ingestions)

Post-hoc analysis of IEM detection by component found:
•The Otsuka cloud server recorded 78.3% (94/120) of IEM ingestions.
•The patches detected 98.3% (118/120) of IEM ingestions.
Latency:
•The mean (standard deviation) time from IEM ingestion to detection by the patch (as registered on the Otsuka cloud server and reported by clinic staff) was 5.1 (3.5) minutes for aripiprazole + IEM tablets ingested without food (Hour 0), 1.4 (0.8) minutes and 1.3 (1.0) minutes for placebo + IEM tablets ingested without food (Hours 2 and 6, respectively), and 1.1 (0.5) minutes for placebo + IEM tablets ingested 30 minutes after the start of a high-fat meal.
Post-hoc analysis of data transfer time between each MIND1 System component found:
•The mean (standard deviation) time from IEM detection by the patch to registration of the ingestion on the Otsuka cloud server was 21.4 (30.1) minutes. Nearly all of the latency occurred during the wireless Bluetooth transmission of data from the patch to the (b) (4) the smart phone.
Safety Results:
•No device-associated AEs were reported during this trial.
•The following treatment-emergent adverse events (TEAEs) were reported in 6/30 subjects: nausea (5/30 subjects), dizziness (1/30 subjects), epistaxis (1/30 subjects), mood swings (1/30 subjects), and vomiting (1/30 subjects). All TEAEs reported were trial medication-associated. All instances of nausea, vomiting, and mood swings were potentially related to the trial medication.
•No subjects discontinued from the trial, including discontinuations due to AEs.
•No deaths or other SAEs were reported during this trial.

•The trial medication-associated AEs observed during the trial were consistent with the known safety profile of aripiprazole.

Reviewer Comment and Conclusion: Results from this study indicate that there is a roughly 20% false negative rate with this device. All subjects took the drug; the Cloud (which is where the monitoring Health Care Provider [HCP] would look to verify compliance) tells the HCP that 1 in 5 doses were missed when in reality these doses had not been missed. If the hypothetical HCP then verified the patch for data, then the HCP would conclude all but 2-3% of the time that the patient had been compliant when, in fact these patients had been 100% compliant. There are no new safety concerns that arise from this study either generally or specifically, because this is not the version of the device that is to be marketed.

6.4. OSMITTER 316-13-206B: A Substudy to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Period

6.4.1. Study Design

Overview and Objective

OSMITTER 316-13-206B, "A Substudy to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Period," was conducted to determine the accuracy of IEM detection by the DW5 Proteus Patch (Patch) following the application of a single Patch to the subject followed by 4 IEM ingestions in the clinic. Otsuka Medical Software application (app) version 1.5.2 was used for all subjects.

The objectives of the study were:
Primary Objective:

- To measure the accuracy of IEM detection by the MIND1 System using the placebo + IEM, and to evaluate the latency period between site-reported ingestion time and detection of the ingestion event by the Patch.

Secondary Objectives:

- To measure the latency period between the Patch detection of the ingestion event and the detection of the event in the Otsuka Cloud-based Server.
- To evaluate the safety of the MIND1 System.

Trial Design

A brief introduction was provided by the clinic staff to explain the app. The site was provided with education and training to pair the Patch with the app. After waiting at least 10 minutes after pairing of the Patch with the compatible computing device (eg, smartphone) app, the

clinic staff placed a Patch on the subject's torso before the first IEM ingestion. The Patch was placed on a subject's body within a predetermined zone, just above the left costal margin, anywhere from the xyphoid to the left midaxillary line. The subject was then instructed to ingest the placebo + IEM. Subjects received the placebo + IEM with approximately 240 mL room temperature, still water. Water was allowed ad libitum, and subjects could eat as they wished over the course of the day. Upon each dosing, a clinic staff member checked the subject's mouth to ensure that the placebo + IEM had been swallowed, and this was documented.

During Visit 1 (Day 1), subjects ingested 1 placebo + IEM approximately every other hour, for a total of 4 ingestions (Hours 0, 2, 4, and 6). Clinic staff recorded the time of each ingestion of an IEM. Clinic staff checked the smartphone at 30-minute intervals for the presence of a timeline ingestion tile and recorded the time it was detected. Following the final IEM ingestion at approximately Hour 6, the subject remained at the trial site until the final ingested IEM was detected by the smartphone, or until 2 hours had elapsed since the final ingestion.

The Patch was an un-medicated adhesive device that was worn on the torso. The Patch detected and time-stamped each placebo + IEM ingestion and measured and recorded other date- and time-stamped physiologic and behavioral data, such as heart rate and levels of physical activity and rest.

Study Endpoints

Assessments of the components in this trial included the recording of the following:

- Time of each ingestion of the placebo + IEM observed by the clinic staff.
- Time that the placebo + IEM ingestion was detected by the Patch and displayed on the smartphone following each ingestion observed by the clinic staff.
- Time of detection of each placebo + IEM ingestion event by the Otsuka Cloud-based Server (server time stamp).

Safety assessments included the following:

- AEs (severity, relationship to the device, outcome, seriousness, and unanticipated device effects).
- Vital signs (heart rate and blood pressure).

The primary endpoints included the following:

- The accuracy of IEM detection by the Patch as a timeline ingestion tile observed by the clinic staff on the smartphone after each scheduled ingestion event, which is measured by the proportion of subjects with IEM detection reported for each of the 4 time points.
- The latency period between the clinical site-reported ingestion time and the signal detection of the ingestion event by the Patch, which is displayed on the smartphone as a timeline ingestion tile after each scheduled ingestion event.

The secondary endpoint was the latency period between the Patch detection of an ingestion event (e.g., the acquisition time stamp) and the detection of this ingestion event in the Otsuka Cloud-based Server (e.g., server time stamp).

An endpoint defined for exploratory analysis was the proportion of subjects who received timeline ingestion tiles on the smartphone within 30 minutes after ingestion.

6.4.2. Study Results

Patient Disposition

Planned enrollment was 30 healthy volunteers; actual enrollment was 29 subjects. Data for all 29 subjects were analyzed. There were no dropouts, deaths or serious adverse events. Subjects included were healthy males or healthy non-pregnant females 18 to 65 years of age with a body mass index (BMI) between 19 and 32 kg/m2 (inclusive).

Results

Primary Endpoints: The first primary endpoint, the proportion of subjects with IEM detection by the Patch as a timeline ingestion tile measured with the system (smartphone) by the clinic staff, is presented in the following table.

Table 1 Proportion of Subjects with Ingestible Event Marker Detection as a Timeline Ingestion Tile Observed by the Clinic Staff on the Smartphone (ITT Sample)

Time Point	N[a]	n[b]	Percent of Subjects With IEM Detected	95% Confidence Interval
Hour 0	29	28	96.6	(82.2, 99.9)
Hour 2	29	27	93.1	(77.2, 99.2)
Hour 4	29	28	96.6	(82.2, 99.9)
Hour 6	29	29	100.0	(88.1, 100.0)

a Number of subjects in ITT Sample ingesting IEM at Hours 0, 2, 4, and 6.
b Number of subjects with IEM detected by the Patch observed through the app on the smartphone at the given time point. Source: CT-5.1.

Secondary Endpoint: The times from Patch detection of ingestion of placebo + IEM to detection of the IEM by the Otsuka Cloud-based Server are presented in Table 3. The latency period (in minutes) from Patch detection (acquisition time) to the time of detection in the Otsuka Cloud-based Server (server time) had mean (SD) times of 7.5 (23.7), 10.3 (20.9), 6.2 (10.4), and 6.2 (8.9) at Hours 0, 2, 4, and 6, respectively. The range of the latency time at all scheduled time points was 0.4 to 123.2 minutes.

Table 2 Table 3 Time from the Patch Detection of Ingestible Event Marker (IEM) to Detection of IEM in the Otsuka Cloud-based Server (ITT Sample)

Time Point	N[a]	Mean latency time (minutes)	Standard Error of Mean	Median	SD	Min	Max	90th Percentile	95th Percentile
Hour 0	28	7.5	4.5	1.8	23.7	0.5	123.2	11.1	36.2
Hour 2	26	10.3	4.1	2.0	20.9	0.5	80.8	38.5	68.4
Hour 4	27	6.2	2.0	1.6	10.4	0.4	31.2	29.7	30.0
Hour 6	29	6.2	1.7	1.9	8.9	0.8	29.7	24.2	28.6

Max = maximum; Min = minimum; SD = standard deviation.
a Number of subjects with IEM detected and information received in the Cloud-based Server at the given time point. Source: CT-5.3.

Safety
There were no deaths, serious TEAEs, discontinuations due to TEAEs, or AEs reported in this trial (source CT-8). There were no clinically significant findings in the laboratory or vital signs results.

Reviewer Comment: All 29 subjects ingested the event marker by hour 6 there was 100% concordance with the Cloud (no false negatives at 6-hours). At hour four 27/29 had been detected. This is a more dependable outcome than study 206A where there appeared to be a roughly 20% failure to transmit to the Cloud. The Applicant states that study 206A informed them to make product changes that were implemented in study 206B. This study was designed to test the device under the ideal conditions of perfect use; this was not a test of the human factors of actual use.

6.5. Protocol No. 316-14-220 Cohort 1A 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

6.5.1. Study Design

Overview and Objective

Protocol No. 316-14-220 Cohort 1A 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 was ongoing at the time of the submission and Trial 316-14-220 is now complete and the remaining safety results (ie, results for Cohort 2, completed on 07 Jul 2015) are now provided in this 120-Day Safety Update. The review strategy for this trial in this NDA is to focus on deaths, serious adverse events, adverse events that lead to study-dropout as numbers are small and the clinical trial database for Abilify is large and well-characterizes the Abilify related adverse event profile.

Trial Design

Reviewer Comment: The design and Methodology are included for the sake of completeness; however, no efficacy [usability] results are reported in this NDA and this was the understanding at the pre-filing meeting. The summary basis of approval of this NDA rests on the results of one usability study referred to in the submission as "Validation Study of the Patient Component (app) of the Otsuka Software"..]

This was an open-label trial to evaluate the usability of the MIND1 System by adult patients with schizophrenia. The trial included one treatment group; there was no control group. The trial included a screening period (≤ 2 weeks), a treatment period (8 weeks), and a safety follow-up period (2 weeks). There were 2 phases of the treatment period: a training phase during the first part of the treatment period and an independent phase during the second part of the treatment period.

Each subject was scheduled to visit the trial site a total of 6 times during participation in this trial: once during the screening period, once at baseline, and 4 times during the treatment period (Weeks 1, 2, 3, and 8). In addition, each subject was scheduled to have 2 telephone contacts (once at the Week 4 time point and once during the safety follow-up period). If a subject withdrew from the trial before Week 8, then an early termination visit was scheduled in lieu of the Week 8 visit.

Number of Subjects: Approximately 32 patients were planned to be enrolled at 6 trial sites in the US.

Diagnosis and Main Criteria for Inclusion: Subjects with schizophrenia, between 18 and 65 years of age (inclusive), who had been prescribed and stabilized on oral aripiprazole at the time of screening.

The versions of the components used in this trial (Cohort 1) were the (b) (4) version IEM and Patch (RP4) combination, with the Otsuka Medical Software Version 1.4. The drug-device combination consisted of a tablet of aripiprazole (10, 15, 20, or 30 mg) plus the embedded IEM.

All patients took aripiprazole + IEM tablets during the treatment period of this trial. In addition, placebo + IEM tablets were used, but for training purposes only during defined scheduled trial site visits.

Subjects discontinued their normally prescribed oral aripiprazole tablets and took the aripiprazole + IEM tablets at the previously prescribed dose during the 8-week treatment period. Aripiprazole + IEM tablets were required to be taken once-daily. Upon completion of participation in the treatment period of the trial, patients stopped taking the aripiprazole +IEM tablets and resumed their normally prescribed oral aripiprazole treatment.

The Patch was an unmedicated adhesive device that was worn on the torso and was designed for 7-day wear. The Patch detected and time-stamped each IEM ingestion and measured and recorded other date- and time-stamped physiologic and behavioral data, such as heart rate and levels of physical activity and rest.

Duration of Treatment: Subjects ingested the aripiprazole + IEM tablets once daily, at their previously prescribed dose, over the 8-week treatment period.

Trial Assessments: The following scales were used to evaluate various aspects of the usability of the MIND1 System:

- Subject Ability to Use System Scale – Healthcare Professional Version; Caregiver Usability Assessment Scale
- Caregiver Involvement Scale; Subject Usability Scale
- Subject Satisfaction Scale
- Healthcare Professional Usability Assessment Scale
- Healthcare Professional Overall Satisfaction Scale.
- Time to first occurrence of the subject being able to replace and pair the Patch independently and successfully, use of the application (by the subject, proportion of days) and use of the healthcare professional portal (by the investigator and/or designated clinical staff, proportion of days)
- Frequency of Call Center support by help type
- The proportion of ingested IEMs registered on digital health data server (versus expected number ingested).

Efficacy assessments included the Clinical Global Impression (CGI) - Severity scale (CGI-S), the CGI - Improvement scale (CGI-I), the Patient Global Impression - Improvement scale (PGI-I), and the Positive and Negative Syndrome Scale (PANSS).

Safety was assessed by collection of adverse events (AEs), device-associated AEs, serious adverse events (SAE)s, AEs leading to discontinuation, unanticipated adverse device effects, the Columbia-Suicide Severity Rating Scale (C-SSRS), vital signs, and laboratory tests.

Criteria for Evaluation: The primary endpoint of this trial was the proportion of patients who were able to replace and pair a Patch independently and successfully by the end of the Week 8 trial visit (or early termination, if applicable), which was evaluated using the Subject Ability to Use System Scale – Healthcare Professional Version.

The secondary endpoint was the proportion of time during the trial period when patients wore their Patches.

Statistical Methods: This trial was exploratory in nature. Approximately 32 patients were planned to be enrolled to produce a 2-sided 95% confidence interval (CI), with a width of 0.298, and a lower limit of 0.621 for the proportion of patients who were able to replace and pair a Patch independently and successfully if the sample proportion was 0.8.

The exact Clopper-Pearson method was used in the sample size calculation, which was based on the binomial distribution. Subjects who did not have any assessments after baseline were counted as failures. The estimated proportion and its 95% CI were provided using the exact Clopper-Pearson Binomial method.

The following analysis samples were defined for this trial:

- Enrolled Sample: All patients who signed an informed consent form and entered the trial;
- Safety Sample: All patients who entered the trial and used the MIND1 System;
- Intent-to-treat (ITT) Sample: All patients who entered the trial and used the MIND1 System (i.e., this was the same as the Safety Sample).

The secondary endpoint, proportion of time during the trial period when patients wore their Patches, was analyzed using data recorded by the MIND1 System (digital health data) and was summarized using descriptive statistics.

6.5.2. Study Results

Compliance with Good Clinical Practices

Safety variables that were analyzed and summarized descriptively included AEs, vital signs, and the C-SSRS.

Table 3 Disposition of Subjects in Study 316-14-220

Subject Disposition - Enrolled Subjects

Number of Subjects	**n**
Screened	38
Enrolled	37
Treated	37
Completed	27
Discontinued	10
Subject withdrew consent to participate	5
AEs	2
Lost to follow-up	2
Protocol deviation	1
Intent-to-treat*	37
Analyzed for safety*	37

*Subjects who entered the trial and used the MIND1 System.
Source: CT -1.1 and CT-2.1.

Safety Results: The majority of patients (24/37 patients, 64.9%) had 50 to 56 days of exposure to the MIND1 System (CT-7.1). Mean (SD) duration of exposure was 47.4 (14.1) days (CT-7.2).

Overall, there were no deaths, 2 serious TEAEs, 1 severe TEAE, and 2 AEs resulting in discontinuation from the trial were experienced by the following 3 patients (Source CT-9.2, CT-9.3):

- Subject (b) (6) (64-year-old black male) experienced a serious, TEAE of transient ischemic attack on Day 23 of the trial, which resulted in hospitalization. The event was not considered related to the IMP/test product. No action was taken regarding the trial treatment; the subject continued in the trial and recovered from the SAE.
- Subject (b) (6) (58-year-old black female) experienced a serious, moderate intensity TEAE of agitation on Day 16 of the trial, which resulted in hospitalization and discontinuation from both the MIND1 System and the trial. The event was not considered related to the IMP/test product. The subject recovered from the SAE.

Reviewer Note: Akathisia is a common and drug-related adverse event associated with Abilify. It appears from the narrative summary that the patient continued to be treated with Abilify for schizophrenia though she was discontinued from the study drug-product. Therefore, this agitation does not appear to be akathisia or drug related; however, this is moot as akathisia is already well-described in labeling.

- Subject (b) (6) (55-year-old black male) experienced a non-serious, severe, device-related TEAE of rash (verbatim term, skin rash at sensor Patch site) on Day 25 of the trial, which resulted in discontinuation from the MIND1 System and from the trial. The subject recovered from the AE.

Adverse Events were classified as either "Device Related", "Medication Related" or Unrelated. Two patients dropped out of the study due to adverse events. There was one device-related adverse dropout and one study-unrelated adverse drop-out Subject (b) (6) (described above).

Overall, 13 of 37 patients experienced device-associated TEAEs. The most frequently occurring device-associated TEAE was pruritus (5/37 patients) One subject had a device-associated TEAE that was considered severe (rash, which lead to discontinuation of Subject (b) (6) (described above) from the trial). Table 1 includes the breakdown of adverse events that were considered device related.

Table 4 Table 1 Incidence of Device-associated, Treatment-emergent Adverse Events by MedDRA Preferred Term and Severity (Safety Sample)

System Organ Class	N=37			
	n (%)			
MedDRA Preferred Term	Mild	Moderate	Severe	Total
Any device-associated TEAEs	--	--	--	**13 (35.1)**
Skin and subcutaneous tissue disorders				
Pruritus	4 (10.8)	1 (2.7)	0 (0.0)	5 (13.5)
Rash	2 (5.4)	0 (0.0)	1 (2.7)	3 (8.1)
Dermatitis contact	2 (5.4)	0 (0.0)	0 (0.0)	2 (5.4)
Erythema	2 (5.4)	0 (0.0)	0 (0.0)	2 (5.4)
Rash erythematous	2 (5.4)	0 (0.0)	0 (0.0)	2 (5.4)
Blister	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)
Infections and infestations				
Abscess	0 (0.0)	1 (2.7)	0 (0.0)	1 (2.7)
Injury, poisoning and procedural complications				
Excoriation	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)
Nervous system disorders				
Paraesthesia	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)

MedDRA = Medical Dictionary for Regulatory Activities.
TEAEs were all AEs that started after the start of the IMP treatment; or if the event was continuous from baseline and was serious, IMP related, or resulted in death, discontinuation, interruption, or reduction of IMP. Device-associated AEs were those reported on the adverse device event page of the CRF. Device-associated AEs could have been associated to any part of the MIND1 System (except aripiprazole). Subjects were counted once, per MedDRA preferred term, for the most severe of multiple occurrences of a specific term.
Source: CT-8.2.2 and CT-8.2.3.

Medication-associated TEAEs were those events reported on the AE page of the CRF. Overall, 12 of 37 patients (32.4%) experienced medication-associated TEAEs. The most frequently occurring medication-associated TEAEs were upper respiratory tract infection and hypertension, which were experienced by 3 patients each (8.1%). No subject had a medication-associated TEAE that was considered severe.

Table 5 Incidence of Medication-associated, Treatment-emergent Adverse Events by MedDRA Preferred Term and Severity (Safety Sample)

System Organ Class	N=37			
	n (%)			
MedDRA Preferred Term	Mild	Moderate	Severe	Total
Any medication-associated TEAEs	--	--	--	**12 (32.4)**
Infections and infestations				
Upper respiratory tract infection	3 (8.1)	0 (0.0)	0 (0.0)	3 (8.1)
Nasopharyngitis	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)
Vascular disorders				
Hypertension	2 (5.4)	1 (2.7)	0 (0.0)	3 (8.1)
Gastrointestinal disorders				
Constipation	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)
Diarrhea	0 (0.0)	1 (2.7)	0 (0.0)	1 (2.7)
Dry mouth	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)
Investigations				
Blood pressure increased	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)
Blood pressure systolic increased	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)
Nervous system disorders				
Transient ischemic attack	0 (0.0)	1 (2.7)	0 (0.0)	1 (2.7)
Psychiatric disorders				
Agitation	0 (0.0)	1 (2.7)	0 (0.0)	1 (2.7)
Respiratory, thoracic, and mediastinal disorders				
Sinus congestion	1 (2.7)	0 (0.0)	0 (0.0)	1 (2.7)

TEAEs were all AEs that started after the start of the IMP treatment; or if the event was continuous from baseline and was serious, IMP related, or resulted in death, discontinuation, interruption, or reduction of IMP. Medication-associated AEs were those events reported on the AE page of the CRF. Subjects were counted once, per MedDRA preferred term, for the most severe of multiple occurrences of a specific term.

Source: CT-8.4.1 and CT-8.4.3.

Trial 316-14-220 was completed during the review cycle and the remaining safety results (ie, results for Cohort 2, completed on 07 Jul 2015) were provided in this 120-Day Safety Update.

In Trial 316-14-220 (Cohort 2), 30 adult patients with schizophrenia were enrolled and treated with TRADEMARK (aripiprazole + IEM, Patch + MDDS, and the Otsuka Medical Software) over an 8-week treatment period. Of the 30 patients in Cohort 2, 22 (73.3%) patients completed the trial, and the remaining 8 (26.7%) patients discontinued from the trial, most frequently due to AEs (4 of 30 patients, 13.3%).

Table 6 Trial 316-14-220 (Cohort 2): Subjects with Discontinuation of Treatment Due to Treatment-emergent Adverse Events (Safety Sample)

Subject Number/ (Age/Gender/Race)	TEAE Preferred Term	Trial Day (Onset of AE)	Serious? (Y/N)/ Severity	Test Product Causality/ Action Taken	Outcome
Device-associated TEAEs resulting in discontinuation of treatment					
(b) (6)/ (61/M/Black)	Rash papular	Day 34	N/ Moderate	Related/ Drug-device withdrawn	Recovered/ resolved
(b) (6)/ (50/F/Black)	Pruritus	Day 1	N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
	Skin discoloration	Day 1	N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
(b) (6)/ (54/F/black)	Rash pruritic	Day 24	N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
Medication-associated TEAEs resulting in discontinuation of treatment					
(b) (6)/ (41/M/Black)	Drooling	Day 31	N/ Moderate	Related/ Drug-device withdrawn	Recovered/ resolved
Source: 120SU-CT-9.3.					

Reviewer Conclusion: There do not appear to be safety results from this trial that would affect changes in the current proposed safety labeling.

7 Integrated Review of Effectiveness

The Applicant was not required to submit an integrated summary of efficacy as they presented no clinical therapeutic efficacy data. The one pivotal trial in this NDA is a Consumer Usability Study. The Applicant for Abilify-MyCite provide a product for review that is an advance in technology (b) (4) The efficacy of the drug substance, Abilify immediate release formulation, is not expected to be affected by the inclusion of the (b) (4) IEM into the tablet; therefore, the efficacy of the drug substance is presumed to be the same for regulatory purposes.

The negotiated requirement for the approval of this claim was that the Applicant provide evidence that the product could be used and would perform as it would be labeled.

The Applicant was required to perform one consumer usability study that demonstrated that trained or untrained correct use of the product was likely possible. The review of this study was performed by the Division of Medication Error Prevention and Analysis (DMEPA). The following is a summary of that review.

Results for Critical Tasks

- 35 out of 36 had use difficulty or task failures(s) (~97%)
    - 19/19 Untrained
    - 16/17 Trained

- Total use difficulties (n=29), Total task failures (n=88)
    - Untrained participants: Difficulties (n=16), Failures (n=58)
    - Trained participants: Difficulties (n=13), Failures (n=30)

Summary & Conclusion of DMEPA Review

- The inability for patients to use the system would likely not allow for accurate measurement of medication adherence

- The critical task failures seen in the HF study could result medication errors in real life setting (e.g., extra doses and missed doses)

- Given the number of critical task failures spread across all user groups, it is not apparent that training or labeling the product for a certain user population in actual use would be an option

- The risks for medication errors have not been adequately addressed and no modifications to the system have been proposed by the Applicant

- The patient user interface remains suboptimal and does not support safe and effective use in the intended population

8 Review of Safety

The safety of Abilify-MyCite is presumed to represent the additive safety of Abilify with the parallel use of the skin patch. The Applicant was therefore not required to pool safety data or provide an integrated summary of safety. The individual trials were reviewed for deaths, serious adverse events, and dropouts as well as adverse events that did not represent safety signals that were already identified from the individual components.

Adverse events that occurred in the Abilify-MyCite development program qualitatively represented adverse events that are already characterized in labeling for the individual

products in this combination.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee was planned; however, a FDA Regulatory Briefing was held on 26 February 2016 wherein the opinion of the DMEPA review was acknowledged and affirmed.

10 Labeling Recommendations

The consumer use study demonstrated that Abilify-MyCite could not be used as labeled. The Abilify (aripiprazole) drug substance labeling need not be modified as a component of the potentially approvable Abilify-MyCite product.

11 Risk Evaluation and Mitigation Strategies (REMS)

No REMS was deemed necessary for the potentially approvable Abilify-MyCite product.

12 Postmarketing Requirements and Commitments

There are currently no post-marketing requirements necessary for the Abilify My Cite product.

13 Appendices

None for this review.

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/s/

PAUL J ANDREASON
03/03/2016
Recommend Complete Response Action

TIFFANY R FARCHIONE
04/23/2016

MITCHELL V Mathis
04/25/2016