Amsterdam, 26 March 2020
EMA/CHMP/431264/2020
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Abilify MyCite

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/005062/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AE	Adverse event
API	Active pharmaceutical ingredient
app	Application
AR	Assessment Report
ASMF AP/RP	Active Substance Master File Applicant´s Part / Restricted Part
BMI	Body mass index
BP1	Bipolar 1 disorder
CE	Conformité Européenne
CF	Clinical figure
CGI-I	Clinical Global Impression - Improvement scale
CGI-S	Clinical Global Impression - Severity
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cm	centimetre
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CS&PV	Clinical Safety & Pharmacovigilance
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Clinical table
DMS	Digital Medicine System
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DW	disposable wearable
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic case report form
eICF	Electronic informed consent form
EMA	European Medicines Agency
ET	Early termination
EU	European Union
F	Female
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare provider
HF	Human factors
HLGT	High level group term
HPLC	High performance liquid chromatography
IADL	Independent Activities of Daily Living scale
IC	Integrated Circuit
ICF	Informed consent form

ICH	International Conference on Harmonisation
ID	Identification number
IEC	Independent ethics committee
IEM, IS	Ingestible event marker, also known as ingestible sensor
IMP	Investigational medicinal product
IRB	Institutional review board
ITT	Intent-to-treat
IWRS	Interactive web response system
kg	kilogram
LOCF	Last observation carried forward
LoQ	List of Questions
M	Male
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
Max	Maximum
MDD	Major depressive disorder
MDDS	Medical Device Data Systems
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minimum
MIND1	Medical Information Device 1
MMRM	Mixed-effect model repeated measurement
MO	Major Objection
N/A	Not applicable
NSR	Non-significant risk
OC	Observed case
OC	Other Concern
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
Otsuka	Otsuka Pharmaceutical Co., Ltd
PANSS	Positive and Negative Syndrome Scale
PD	Pharmacodynamics
PDA	Positive detection accuracy
PI	Product Information
PGI-I	Patient Global Impression - Improvement scale
PK	Pharmacokinetics
Proteus	Proteus Digital Health® Inc.
PSP	Personal and Social Performance scale
QUAL	quality
RMP	Risk management plan
RP	re-usable patch
RPM	Rotations per minute
SA	Scientific Advice
SAE	Serious adverse event

SAP	Statistical analysis plan
SAUSS	Subject Ability to Use System Scale
SAUSS-HCP	Subject Ability to Use System Scale – Healthcare Professional Version
SAWP	Scientific Advice Working Party
SCH	Schizophrenia
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TLC	Thin-layer chromatography
ULN	Upper limit of normal
US	United States
WOCBP	Women of childbearing potential

1. Joint Rapporteur Recommendation

Based on the review and the applicant's response to the CHMP list of questions on quality, safety and efficacy, the application for Abilify MyCite in the following indication:

"Abilify MyCite is a drug-device combination product comprised of aripiprazole tablet embedded with an ingestible sensor to measure medication adherence.

Abilify MyCite is indicated in adults for the treatment:

- *of schizophrenia,*
- *of moderate to severe manic episodes in bipolar I disorder and*
- *for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment."*

is not approvable since "major objections" still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of outstanding issues (Section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the list of outstanding issues.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

General/Overarching

- Based on the *in vitro* dissolution data provided, comparability of the applied product and Abilify® tablets, the reference product for this hybrid application, cannot be concluded.

Quality:

- The methodology of the IEM activation test has not been sufficiently justified. Validation of the test is not seen as appropriate to ensure consistent quality of the finished product.
- The acceptance criteria for the IEM activation test are not accepted. To ensure a defined and consistent quality of the finished product, a defect rate as low as reasonably possible should be implemented in the specification.
- Considering that the medicinal product and the ingestible device form a single integral product, the relevant Essential Requirements for assessment of the safety and performance of the device used with the medicinal product have to be provided in the quality part of the dossier.
- Based on current regulatory requirements, a new MO regarding nitrosamine impurities is raised.

Clinical:

- Due to the paucity of studies, there are major uncertainties on the therapeutic benefit of the Abilify MyCite System. In addition, safety has not been sufficiently characterised.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

N/A

GCP inspection(s)

N/A

New active substance status

Not applicable. Aripiprazole is not a new active substance.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The applicant applied for the following indication:

"*Abilify MyCite tablet with sensor is a drug-device combination product comprised of aripiprazole tablets embedded with a sensor to* ***measure medication adherence****.*

Abilify MyCite is indicated ***in adults*** *for:*

- *the treatment of schizophrenia;*
- *for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment;*
- *the treatment of moderate to severe manic episodes in BP1."*

2.1.2. Epidemiology and risk factors, screening tools/prevention

Schizophrenia is among the most disabling and economically catastrophic medical disorders, ranked by the World Health Organization as one of the top 10 illnesses contributing to the global burden of disease. Schizophrenia is a mental disorder characterized by disruptions in thought processes, perceptions, emotional responsiveness, and social interactions. Although the course of schizophrenia varies among individuals, schizophrenia is typically persistent and can be both severe and disabling.

Precise prevalence estimates of schizophrenia are difficult to obtain due to clinical and methodological factors such as the complexity of schizophrenia diagnosis, its overlap with other disorders, and varying methods for determining diagnoses. Given these complexities, schizophrenia and other psychotic disorders are often combined in prevalence estimation studies. Estimates of the international prevalence of schizophrenia among non-institutionalized persons is 0.33% to 0.75% (Saha et al. 2005, Moreno-Küstner et al. 2018).

Schizophrenia is more common among males than females and also commonly starts earlier in men. People with schizophrenia are 2-3 times more likely to die early than the general population. This is often due to physical illnesses, such as cardiovascular, metabolic and infectious diseases (WHO 2018).

Bipolar affective disorder is a multicomponent illness involving episodes of severe mood disturbance, neuropsychological deficits, immunological and physiological changes, and disturbances in functioning. It is one of the leading causes of disability worldwide and is associated with high rates of premature mortality from both, suicide and medical comorbidities (Rowland and Marwaha, 2018). Epidemiological studies suggest a lifetime prevalence of around 1% for bipolar type I disorder in the general population (Bebbington and Ramana, 1995; Pini et al. 2005).

2.1.3. Clinical presentation, diagnosis and stage/prognosis

Symptoms of **schizophrenia** include psychotic symptoms such as hallucinations, delusions, and thought disorder (unusual ways of thinking), as well as reduced expression of emotions, reduced motivation to accomplish goals, difficulty in social relationships, motor impairment, and cognitive impairment.

Bipolar I disorder can cause dramatic mood swings. During a manic episode, people with bipolar I disorder may feel high and on top of the world, or uncomfortably irritable and "revved up." During a depressive episode, they may feel sad and hopeless. There are often periods of normal moods in between these episodes. Bipolar I disorder is diagnosed when a person has a manic episode.

Schizophrenia and BP1 are among the most severe mental illnesses, with excessive physical comorbidity and greatly reduced life expectancy compared with the general population (De Hert et al. 2011). The active phases of the disorders are associated with highly debilitating symptoms; severe manias and schizophrenic psychosis cause serious behavioural disturbances. Active psychosis has been ranked among the most disabling disorders by severity in the general population, and more disabling than paraplegia, blindness, or HIV infection (Ustün et al. 1999). The majority of patients experience a chronic relapsing-remitting course of the disorders (Bromet and Fennig, 1999; Altamura et al. 2011).

Studies of adherence suggest further that there is a correlation between non-adherence and poor outcomes for the patient. Medication non-adherence in particular, is thought to raise the risk of psychotic relapse by a factor of three to five, and in schizophrenia is associated with rehospitalisation and poor quality of life with the risk of suicide nearly four times higher in service users who are poorly adherent (Brand et al. 2013). In bipolar disorder, there is a similar association with relapse, hospital admission and suicide (Clatworthy et al. 2007; Lage and Hassan, 2009).

2.1.4. Management

Schizophrenia is a treatable disease (WHO). Treatment options for management of schizophrenia can be broadly classified as antipsychotic medications, electroconvulsive therapy (ECT), adjunctive medications and psychosocial interventions (Shah et al. 2017).

The goals of schizophrenia therapy vary with the phase and severity of illness. In the acute phase (i.e., the initial psychotic episode or a psychotic relapse with a prior history of schizophrenia), the goal is to reduce the severity of psychotic thoughts and behaviours. The first-line medication treatment for schizophrenia are antipsychotic medications, which have been shown to be effective in treating symptoms and behaviours associated with the disorder. Most of the antipsychotic drugs need to be increased gradually before reaching a therapeutic dose. The antipsychotic drugs used for the treatment of schizophrenia include quetiapine, clozapine, iloperidone, haloperidol, risperidone, paliperidone, ziprasidone, asenapine, lurasidone, aripiprazole and olanzapine. There are also rapidly dissolving formulations (for risperidone, olanzapine, asenapine, and aripiprazole) available for patients who are

willing to take a pill by mouth, but either cannot or do not swallow it. For uncooperative patients or patients who do not want to take oral antipsychotics, there are injectable IM antipsychotics available (e.g., haloperidol, olanzapine, aripiprazole, and ziprasidone) (Stroup and Marder, 2019).

In the maintenance phase, the psychotic symptoms are usually well controlled. In this phase, the goal of the treatment is to minimize symptoms and functional impairments, avoid relapses, and promote recovery that allows self-determination, full integration into society, and pursuit of personal goals. The antipsychotic medication should be continued indefinitely in this phase, even if patients have achieved remission from a first psychotic episode. In this phase, long-acting injectable antipsychotics may be useful for patients with schizophrenia who experience frequent relapses due to non-adherence to antipsychotic medications (Stroup and Marder, 2019).

Psychosocial interventions may be used in conjunction with antipsychotic drug therapy. These interventions are used in the acute phase to reduce excessively stimulating or stressful life events. In the stabilization phase, assistance may be needed with the transition from an inpatient setting to living in the community (Lehman et al. 2004).

Bipolar disorder is a mood disorder that is characterized by periods of pathologic mood elevation (mania or hypomania). Patients with bipolar I disorder experience manic episodes and nearly always experience both hypomanic episodes and major depressive episodes (Shelton and Bobo, 2019).

In general, most of the patients with **Bipolar disorder** are managed on the outpatient setting. However, some patients may require inpatient care. Treatment options for management of BP can be broadly classified as mood stabilizers (lithium, valproate, lamotrigine, carbamazepine/oxcarbazepine and topiramate), antidepressants, antipsychotic medications (e.g. olanzapine, quetiapine, aripiprazole, risperidone, paliperidone, amisulpiride, asenapine, ziprasidone and haloperidol), electroconvulsive therapy (ECT), adjunctive medications and psychosocial interventions. Use of various treatment options is guided by the phase of illness (mania/hypomania/depression/mixed) in which patient presents to the clinician and past treatment history (Shah et al. 2017).

One of the greatest problems clinicians face when dealing with chronic illnesses is the effectiveness of treatment. This is determined by various different factors such as patient tolerance of the drug, the appropriateness of the regimen, and, above all, adherence to the treatment prescribed.

The issue of low/undetectable medication adherence is considered of significant clinical relevance in psychiatry. In order to improve adherence, reduce gaps in therapy, and prevent relapse compared with oral antipsychotics long-acting injectable (LAIs) antipsychotics were developed. The first LAIs, fluphenazine enanthate and decanoate, were introduced in the 1960s. Numerous LAI antipsychotics have been developed and marketed in the meantime. Aripiprazole 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.

However, there is room for improvement of medication adherence and therefore an unmet medical can be assumed.

2.2. About the product

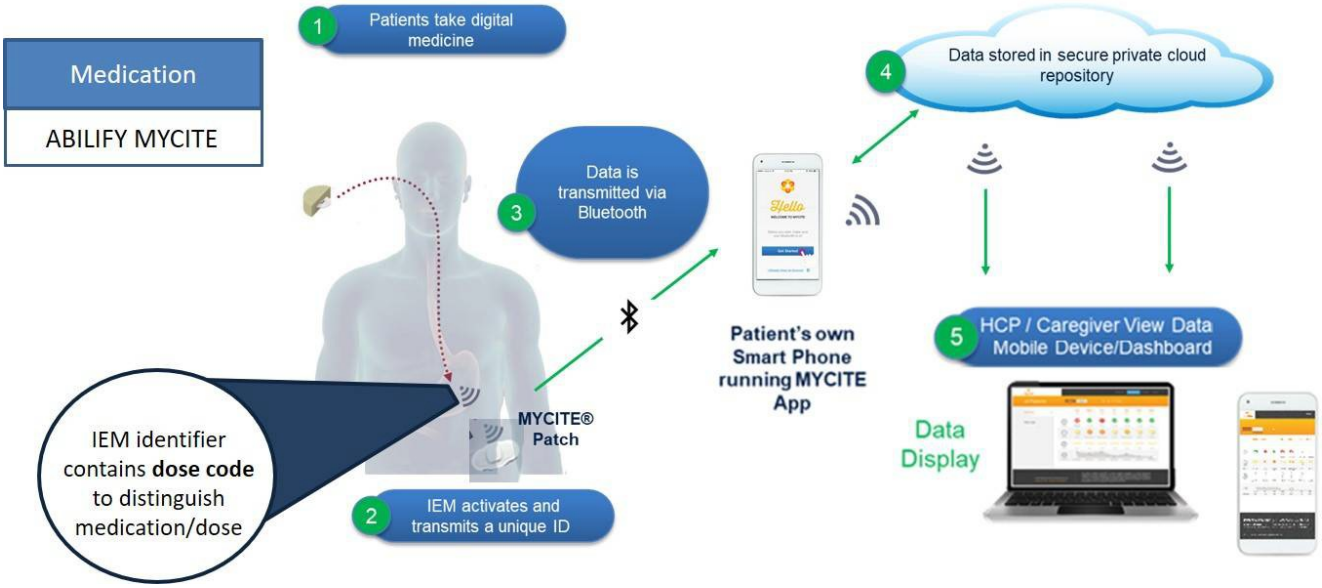
Abilify MyCite is novel drug-device combination product developed by Otsuka and Proteus. The product is composed of the centrally approved Abilify tablets (active substance: aripiprazole) in which an ingestible sensor (IS or IEM) is embedded. Once ingested, the sensor is activated and communicates a unique identifier code of each tablet dose that distinguishes medication and dosage with a Personal Monitor (wearable sensor, also called Patch). The Patch transmits these data (date and time of

ingestion) to a medical software application (the App) allowing – according to the applicant - patients to manage and review medication adherence.

Thus, the Abilify MyCite System is composed of the following components:

- Aripiprazole tablet (centrally approved Abilify) embedded with a sensor (Abilify MyCite)
- Patch: a personal wearable monitor that is made up of a data pod and an adhesive strip. The Personal Monitor detects the sensor upon ingestion and also records physiological and behavioural metrics (i.e., heart rate, activity level, step count, and body angle) and transmits this data to a compatible mobile device.
- MyCite App: a smartphone application (app) used with a compatible smartphone to display information for the patient
- Web-based portal for healthcare professionals (HCPs) and caregivers to view the patient´s data

The distinct components of the overall system, referred to as Abilify MyCite System in this application, are shown in Figure 1 below.



IEM = ingestible event marker, also known as ingestible sensor (IS); ID = identification number.

Source: Figure 2.2-1 Abilify MyCite System

Figure 1: **Abilify MyCite System**

The indication applied for Abilify MyCite is different from the approved indication for Abilify tablets without sensor, with respect to demography (i.e. adolescents are not included) and the additional claim to measure medication adherence.

Hence, the proposed indication is:

"Abilify MyCite is indicated in adults for

- *the treatment of schizophrenia;*
- *the treatment of moderate-to-severe manic episodes in Bipolar I Disorder;*

- *the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.*

"Abilify MyCite is a drug-device combination product comprised of aripiprazole tablets embedded with a sensor to measure medication adherence".

Aripiprazole, the active substance of Abilify MyCite, belongs to the pharmacotherapeutic group of psycholeptics, other antipsychotics (ATC code: N05AX12).

It has been proposed that aripiprazole's efficacy in schizophrenia and bipolar I disorder is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism of serotonin 5-HT_{2A} receptors.

The dosing recommendations for Abilify MyCite are the same as approved for Abilify tablets without sensor.

Of note:

In earlier documents as well in both clinical trials included in this submission, the drug-device product has been referred to as **M**edical **IN**formation **D**evice **1 (MIND1)** or **D**igital **M**edicine **S**ystem **(DMS)**. MIND1 and DMS do not represent the proposed trade name and are referred to as Abilify MyCite in this submission.

The medical device components (ingestible sensor, Personal Monitor and MYCITE App) have been separately registered via European Conformity (CE) assessment procedure by a notified body (NB) of the British Standards Institute in order to obtain CE marks. The applicant provided the "Declarations of Conformity" for each medical device.

2.3. The development programme/compliance with CHMP guidance/scientific advice

According to the applicant, the Abilify MyCite clinical development programme consisted of 6 clinical exploratory trials, and 9 human factors (HF) studies. Out of these studies, only the two clinical studies, trial 316-13-215 and trial 316-14-220, are submitted within the current MAA, as the applicant only considers these two studies relevant for the present MAA.

- **Trial 316-13-215**: A Multicenter, 8-week, Open-label, Single-Arm, Exploratory Trial to Assess the Functionality of an Integrated Call Center for the Digital Medicine System by Adult Subjects With Schizophrenia (SCH), Major Depressive Disorder (MDD), or Bipolar 1 Disorder (BP1) who are Treated With Oral Aripiprazole.
- **Trial 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.

The other 4 exploratory studies, briefly described in this submission, are as follows:

- **Trial 316-13-204**: A Formative Usability Study of the Otsuka MIND1 Prototype by Subjects With Bipolar Disorder or Major Depressive Disorder.
- **Trial 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.

- **Trial 316-13-206a**: A Sub-study to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Period.
- **Trial 316-13-206b**: A Sub-study to Measure the Accuracy of Ingestible Event Marker (IEM) Detection by the Medical Information Device #1 (MIND1) System and Determine the Latency Period.

Over the course of the clinical development programme several EMA **scientific advices** were sought (by Proteus and partnering companies) for the Proteus system and its intended use to measure medication adherence.

Table 1

Scientific Advices	**Investigational product**	**Intended use/claimed indication**	**Digital Medicine system used**
EMA/CHMP/SAWP/768960/2012 *(Proteus partnering with Otsuka Frankfurt Research Institute GmbH):*	*Proteus (then called Raisin) system plus Aripiprazole*	To assess aripiprazole utilisation by recording aripiprazole ingestion as an aid to monitoring aripiprazole adherence in schizophrenic patients.	The sensor was inserted into the Abilify tablet.
EMA/CHMP/SAWP/513571/2015 *(Proteus)*	*Proteus system*	CHMP qualification opinion on ingestible sensor system for medication adherence as biomarker for measuring patient adherence to medication in clinical trials.	IEM: no description provided Signal : no information provided concerning the sent signal length Patch: 10.2 x 5.6 x 0.98 cm

The main conclusions of the CHMP, in particular, with regard to the claimed use of the Proteus system to measure patient adherence, are summarized as follows:

1) EMA/CHMP/SAWP/18795/2011

The claimed indication was: *"[Drug product] is equipped with ingestible microsensor technology **to allow accurate measurement of medication administration events (adherence)"***

CHMP noted that this question was very broad in nature as it refers to 'any drug' product potentially over-encapsulated with the IEM carrier. The CHMP further stated that in any registration process, the would have to be considered as a medicinal product (= new pharmaceutical form), and definitely not as measuring (or 'diagnostic') device per se, as then proposed by the Company. It was further highlighted that the change of formulation of a licensed medicinal product (for which the risk/benefit ratio has been found to be positive) would require thorough re-assessment of the risk/benefit ratio.

Some specific comments regarding the proposed wording were also made:

The CHMP stated that any future description would have to be brief and concise and should not be worded to imply any benefits beyond mere functionality. The statement of "accurate" measurement was considered superfluous and somewhat arbitrary, since the clinical relevance of the Company's threshold of ">90%" has not been adequately justified.

In addition, the CHMP stated, that the term "adherence" describes a highly complex situation in the relationship between patient and healthcare provider. From the data presented, it could only be concluded that the IEM would probably be able to provide data about "taking and scheduling" adherence. It was further referred to the working report of the WHO (2013) "Adherence to long-term therapies: evidence for action (2003)" where it was stated that "…adherence also encompasses numerous health-related behaviours that extend beyond taking prescribed pharmaceuticals…". In this process, the patient is seen as an active collaborator as opposed to "…a passive, acquiescent recipient of expert advice". Repeatedly, CHMP emphasized the point that adherence includes the patient's agreement to the recommendations and that not all dimensions of "adherence" can be measured by the IEM. Therefore, the use of this term was considered ambiguous and possibly misleading within the scope of a description of functionality.

The applicant followed the SA recommendations to restrict the label claim to the drug product which is intended to be licensed in combination with the Proteus technology, in this case Abilify (aripiprazole). Concerning the proposed indication, the advice not to include the wording "accurate" for measurement of adherence was followed.

2) EMA/CHMP/SAWP/768960/2012 (Proteus partnering with Otsuka Frankfurt Research Institute GmbH):

Scientific advice was sought for aripiprazole combined with the Ingestible Event Marker and the Proteus Personal Monitor (the Proteus Raisin System) intended ***to assess aripiprazole utilisation by recording aripiprazole ingestion as an aid to monitoring and/or even support aripiprazole adherence in schizophrenic patients.***

Although no specific request for advice on the clinical development program was formulated (the advice focused on the quality development program), the applicant provided data on patient exposure: The EMITTER psychiatry study that enrolled 28 subjects with schizophrenia and bipolar disorder who carried the device for 28 days.

The CHMP commented that psychotic patients may have difficulties in accepting to be "monitored" and even potentially worsen, with additional productive psychotic symptoms when being felt to be "under observation". It was therefore, further proposed to evaluate the acceptability of the device (overall compliance) and therapeutic performance in a larger population. The CHMP also noted that both, tolerability and potential development of additional symptoms, might impact the benefit/risk assessment especially if the applicant claims an increase in adherence in the longer term. The applicant was advised to seek clinical advice on how to prove therapeutic performance and benefit-risk ratio similar to Abilify.

The applicant followed this EMA-SA to some extent as in Study 316-13-215 also patients with BP1 and MDD were included in addition to patients with Schizophrenia. However, the overall acceptability (overall compliance) and therapeutic performance was not properly investigated (only the functionality of a call center was assessed). The concerns of CHMP that the symptoms of psychotic patients might worsen when being felt to be "under observation" were neither addressed nor discussed in the dossier. No additional clinical SA was sought. In the present submission however, the applicant does not claim anymore that Abilify MyCite supports or increases adherence.

3) EMA/CHMP/SAWP/513571/2015 (Proteus)

Proteus requested an opinion considering the use of the Proteus technology as a "qualified method" ***for measuring adherence and associating relevant physiologic and behavioral parameters, such as indications of therapeutic response***. The Company claimed that when medication is co-ingested with the IEM or taken as part of an integrated (single entity) drug-device dose, Proteus technology is fit-for-purpose to measure medication adherence and associate other data useful in assessing therapeutic response.

The CHMP agreed in considering the use of the Proteus technology (IS) as a qualified method for measuring adherence in clinical trials. The CHMP qualification opinion however referred to the "…acceptability of a specific use of a method, such as the use of a novel methodology or an imaging method in the context of research and development. The method can apply to non-clinical or to clinical studies, such as the use of a novel biomarker. The opinion is based on the assessment of data submitted to the Agency".

The CHMP also commented, that if the IS is intended to be marketed with a specific medicinal product, a relevant benefit/risk assessment will be carried out at time of marketing authorization application depending on the dossier.

There is no specific CHMP guidance for proving the usability/functionality of digital drug-device combinations, such as of Abilify MyCite.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

A QP declaration confirming GMP compliant manufacturing of the drug substance at the proposed drug substance manufacturing sites has been provided.

For the manufacturer of bulk tablets, a manufacturing authorisation and a GMP certificate issued by the Japanese Ministry of Health are available. A manufacturing authorisation and a GMP certificate, have been submitted for the batch releaser

Quality control testing sites: GMP compliance is covered by EUDRA GMP certificates.

GLP

A review of available published literature (October 2008 to January 2019) was conducted by the applicant. However, the applicant cannot claim GLP compliance to any of the published studies.

GCP

According to the applicant, studies 316-14-220 and 316-13-215, both conducted in the USA, are compliant with the principles of Good Clinical Practice (GCP) as defined by the International Conference on Harmonisation (ICH). No GCP inspections have been conducted or are planned for these trials.

GCP compliance for the other four clinical studies (trial 316-13-204, trial 316-13-205, trial 316-13-206a and trial 316-13-206b) and the 9 Human Factor studies cannot be claimed.

2.5. Type of application and other comments on the submitted dossier

Legal basis

This marketing authorization application (MAA) for Abilify MyCite 5-, 10-, 15-, and 30-mg tablets with sensor is made according to Article 10(3) of the Directive 2001/83/EC as amended, a "hybrid

application". The reference product for this application, Abilify® tablets (MAH: Otsuka Pharmaceutical Netherlands B.V.), was centrally approved in the EU on June 4th 2004 (EMEA/H/C/000471).

Abilify MyCite consists of Abilify® tablets (active substance: aripiprazole) embedded with an ingestible sensor (IS or IEM), a compatible Personal Monitor (Patch), and software applications (i.e. MyCite App, Cloud). Abilify tablets with and without an ingestible sensor are manufactured in the same strengths and by the same manufacturer as the approved Abilify tablets (5, 10, 15, and 30 mg). The composition of the proposed tablets is qualitatively and quantitatively identical to the Abilify tablets, except for the addition of the IEM, different amounts of lactose and ten-fold reduced amounts of colorants.

The applicant proposed a new pharmaceutical form "tablet with sensor" for Abilify MyCite to differentiate it from the approved Abilify® tablets. As there are also differences between the therapeutic indications, the applicant submitted a "hybrid" application.

Thus, all non-clinical and clinical aspects relating to the active substance aripiprazole are cross-referenced to the Marketing Authorization for Abilify® (EMEA/H/C/000471).

To support the planned MAA for the Abilify MyCite system and the additional proposed claim of measuring medication adherence, two additional clinical trials (studies 316-13-215 and 316-14-220) were submitted. In addition, to confirm that insertion of the sensor had no impact on physicochemical and biological properties of the proposed combination product and to show bioequivalence between Abilify tablets with and without sensor, two comparative *in vitro* dissolution studies were performed.

The medical device components (ingestible sensor, Personal Monitor and MYCITE App) have been separately registered via European Conformity (CE) assessment procedure by a notified body (NB) of the British Standards Institute in order to obtain CE marks (please refer to the Quality AR and LoQ for further details with this respect). The legal basis for the medical devices included in this submission are Article 1(2)(a) of Directive 93/42/EEC and Article 1(2)(c) of Directive 90/385/EEC.

The medical device components described here are essential elements for the functionality of the total system (Abilify MyCite System).

PRIME

N/A

Accelerated assessment

N/A

Conditional marketing authorisation

N/A

Marketing authorisation under exceptional circumstances

N/A

Biosimilarity

N/A

Additional data exclusivity/ marketing protection

N/A

Orphan designation

N/A

Information on paediatric requirements

N/A

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as tablet with sensor containing 5 mg, 10 mg, 15 mg, and 30 mg of Aripiprazole as active substance. Each tablet contains one Ingestible Event Marker (IEM, sensor) which is a class IIa medical device integrated in the medicinal product.

Other ingredients are: lactose monohydrate, maize starch, microcrystalline cellulose, magnesium stearate and coloring agents.

The product is packaged in opaque, high density polyethylene (HDPE) bottles, induction heat-sealed, and capped with continuous thread (CT) child-resistant closure with desiccant and coiler. One bottle contains 30 tablets with sensor.

Additional medical devices are part of the presentation of the medicinal product: a personal monitor including adhesive strips, wearable sensor and reusable pod with software components are co-packaged as non-integral devices.

3.1.2. Active Substance

An ASMF (Version 5AP and 4RP) for aripiprazole (anhydrous) has been provided by The ASMF contains separate sections on drug substance manufactured for oral- and parenteral dosage forms. Abilify MyCite is an oral dosage form. Accordingly, the parts of the ASMF relating to parenteral dosage forms have not been assessed.

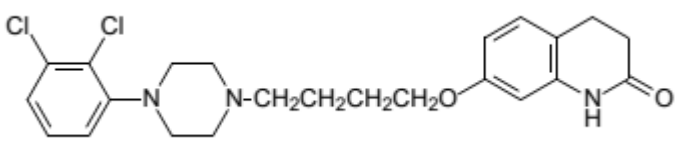
Please note that concerns regarding the Restricted Part of the ASMF are addressed in a separate confidential Annex.

General Information

The drug substance is aripiprazole (anhydrous).

Figure 2

Structural Formula:



Molecular Formula:

$C_{23}H_{27}Cl_2N_3O_2$

Molecular Mass:

448.39

The drug substance is a white crystalline powder. It is practically insoluble in water, soluble in methylene chloride and very slightly soluble in ethanol (96 per cent). is manufactured (for clinical batches and commercial batches). The drug substance does not exhibit stereoisomerism.

Manufacture, process controls and characterisation

Manufacture

Two drug substance manufacturing sites are proposed.

It is confirmed that the manufacturing process is the same for both sites. The presented batch data demonstrate that drug substance of similar quality is manufactured at both sites.

The drug substance manufacturing process consists of two chemical transformation steps.

Characterisation

Structure:

The structure of the drug substance has been elucidated applying standard methods (UV, IR, NMR, MS and XRPD). The relationship between the polymorphic- and solvate form of the drug substance and the proposed process parameters has been investigated in order to ensure that drug substance of non-solvated polymorphic form is consistently manufactured. Stability of the polymorphic form over the retest period has been confirmed in the course of formal stability testing. The drug substance does not exhibit stereoisomerism.

Impurities:

Potential related substances are indicated. Batch analytical data on historical batches of laboratory-, pilot and commercial scale (manufactured according to the current process) are presented. For 17 batches (manufactured from 1999 – 2000) of the proposed commercial scale process tested only two of the potential impurities (have been detected (at or below the reporting threshold of 0.05%). These impurities correspond to Ph.Eur. impurities E and G. Total impurities were very low too (max. 0.08%). These findings have been confirmed for 3 batches manufactured in 2004 and 10 batches manufactured more recently, for which results are presented in S.4.5. (Ph.Eur. impurity E) and (Ph.Eur. impurity E) are controlled in the drug substance as unspecified impurities according to Ph. Eur. 2617 (aripiprazole).

The presented data on related substances are derived from batches manufactured at factory only. A similar impurity profile has been shown for the other proposed manufacturing site, by analytical data on 3 commercial scale batches from 2004 and 10 more recent batches.

It is noted that above discussed results have been generated using two different in-house HPLC methods. However, equivalence of these methods and the now applied Ph.Eur method has been demonstrated (6 drug substance batches have been controlled with the historical in-house methods and the Ph.Eur. method).

Residual solvents are sufficiently controlled by the loss on drying test included in the drug substance specification (limit: NMT 0.5% w/w). Yet, control of solvents should be discussed.

No elemental catalysts, reagents or process aides are used. Inorganic impurities are controlled in the drug substance by a test on sulphated ash according to Ph.Eur. 2617 (aripiprazole).

A detailed discussion on mutagenic impurities is provided. An appropriate control strategy is in place.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification, Analytical Methods, Method Validation and Batch Analyses

The proposed drug substance specification complies with Ph.Eur. 2034 (substances for pharmaceutical use) and 2617 (aripiprazole).

Process related impurities that are not covered by the Ph.Eur. monograph for aripiprazole have not been identified during drug substance characterisation (see above).

Microbiological quality is not tested. Taking into account that the drug substance is a dry powder the risk emanating from microbiological growth is considered to be negligible. Accordingly, omission of microbiological testing is acceptable.

Ph.Eur. methods are applied. Accordingly, no validation data are required. Batch results for six production batches, manufactured in 2014, confirm compliance with Ph.Eur.

Information on the control of the drug substance and used reference standards by the applicant is insufficient.

Reference Standards

(Primary) reference standards have been characterized in detail (incl. identity by NMR, UV and IR as well as related impurities by HPLC, water content by K.F. and assay by titration). Moreover, every lot of the reference standard is qualified against the Ph.Eur. reference standard.

Container Closure System

Aripiprazole drug substance is packaged in a polyethylene bag, closed with a tie-wrap, which is then heat-sealed in a foil bag. The foil bag is stored in a fibre drum with a secure fitting lid. The primary packaging material is made of LDPE and complies with regulation (EU) 10/2011. Considering that the drug substance is in solid state this is sufficient. Appropriate specifications for primary and secondary packaging materials are provided.

Stability

Stability testing has been performed according to ICH conditions (general case according to ICH Q1A) and additional stress studies (including photostability according to ICH Q1B). 3 production scale batches of each of the proposed manufacturing sites have been tested. Stability studies have been completed.

All stability indicating parameters of the drug substance specification have been tested. Only the test on sulphated ash has been omitted, which is acceptable. It is noted that the drug substance specification has been revised after completion of the stability studies. However, the only significant difference regarding stability testing is that the limit for total related substance has been tightened from NMT 0.30% to NMT 0.20%. This tighter limit has actually not been exceeded. The other changes to the drug substance specification are not relevant, because non-stability indicating parameters have been eliminated or acceptance criteria have been widened. Equivalence of the in-house methods that

have been used to determine assay and related substances and the respective Ph.Eur. methods has been shown.

The presented results indicate that the drug substance remains stable under any tested condition. No trends are seen and only little variation is observed. Additional stability results - determined according to Ph.Eur. – from the on-going stability program are provided. The data support the proposed retest period.

The site of manufacture has no impact on the stability profile.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

The dosage form of the proposed product is "tablet with sensor", which is a new standard term (added to EDQM Standard Term Database on March, 5th, 2019). The new pharmaceutical form is not yet included in the Ph. Eur. monograph on tablets. Four different strengths concerning the active pharmaceutical ingredient Aripiprazole have been defined: 5 mg, 10 mg, 15 mg, and 30 mg. The product is packaged in opaque, high density polyethylene (HDPE) bottles, induction heat-sealed, and capped with continuous thread (CT) child-resistant closure with desiccant and coiler. Each tablet contains one Ingestible Event Marker (IEM, sensor) which is a class IIa medical device integrated in the medicinal product.

According to the application form, three different presentations will be marketed: HDPE bottle in cartons of 30 tablets with sensor, HDPE bottle of 30 tablets with sensor with 6 disposable adhesive strips with an embedded battery and one reusable pod ("starter pack" or "treatment initiation pack", to be clarified) and HDPE bottle of 30 tablets with sensor with 6 adhesive strips with embedded battery ("maintenance pack"). Information on the identification of integral (IEM) and non-integral co-packaged medical devices (adhesive strips, reusable pod, software components) has been provided, but needs to be indicated in the correct dossier sections. It is noted that based on the information provided, none of the clinical studies filed for marketing authorisation was performed with the patch (strips) and pod version proposed for the commercial product.

Pharmaceutical development

The qualitative and quantitative composition of the proposed finished product is identical to that of the currently marketed Abilify tablets, with the exception of the amount of colorants, and the insertion of the IEM into the tablet. The composition of the 4 different tablet strengths is not dose-proportional. Compatibility of the drug substance with excipients and functions of excipients has to be amended in the dossier. Decrease of the quantity of the colorants to one tenth compared to the composition of Abilify tablets has been justified.

Main topic of pharmaceutical development was the IEM (sensor) embedded in the tablet. A comprehensive risk assessment for the tablet with the IEM covering factors with medium (weight variation, content uniformity, impurities, description and friability) and high initial risk was performed. Based on development, batch, process validation and stability data, it was concluded that risk associated with weight variation, content uniformity, impurities, description and friability to be sufficiently mitigated.

Two different primary packaging materials, HDPE bottle with desiccant and aluminium-aluminium blister, were evaluated. The HDPE bottle with desiccant was chosen as commercial packaging to ensure sufficient protection from humidity.

IEM content (one IEM per tablet) and IEM functionality at release and during shelf-life were identified as high-risk parameters. The supplier of the IEM, Proteus Digital Health, has developed an IEM activation test, to determine the lifetime of the sensor. Influence of compression force, freeze-thaw testing and different process in the manufacturing of the IEM were evaluated. In all trials failure rate was evaluated. Confirmation was given that IEMs used in commercial product will be auto-singulated.

Sufficient information was given how a possible misuse of the product (e.g. provoking a positive detection signal by dissolving the tablet outside the body near the patch/pod) can be excluded.

It has been confirmed that no changes in the design (composition, technical specification, dimensions) other than programming have been made during development work. The applicant has confirmed to follow the relevant EU Variations Regulation and associated variation guidelines in place.
Section 3.2.P.2 should be amended with the information which IEM version (type, programming, way of singulation etc.) has been used for the different development, process validation, stability and usability/clinical studies, preferably in a tabular format. The same applies for non-integral co-packaged medical devices (patch, pod, software). Compatibility with these non-integral devices was not discussed at all in Pharmaceutical Development. Relevant quality information for the non-integral medical devices should be given, in the context of the device reproducibly delivering the signal and information to the patient and therefore influencing the correct administration of the required dose of the medicinal product.

Relevant regulatory information on medical devices is discussed below (Regional information / Medical Devices).

Manufacture of the product and process controls

Manufacture

Bulk Aripiprazole + IEM tablets are manufactured by a named manufacturer. Primary packaging, secondary packaging, kit assembly and final batch release is performed by a named manufacturer. Quality control testing sites are named.

The flow chart and the description of the manufacturing process provided are covering the complete manufacturing process. Yields for the different process steps have been defined for the commercial routine process.

Process controls

Process control needs to be more clearly defined. Critical process parameters and corresponding in-process controls should defined be in line with controls applied during process validation

The submitted specification for the sensor (IEM should be justified and amended with any parameter relevant to assure function of the IEM. The sensor as being an integral part of the tablet has to be defined more clearly throughout dossier (3.2.P.1, 3.2.P.3.2).

Process validation / verification

The manufacturing process of the tablet includes a critical and novel step, the positioning of an IEM between two tablet layers. The process is therefore considered as a non-standard process. A comprehensive process validation report covering three commercial size batches per tablet strength was submitted. Process parameters and equipment used are described in sufficient detail. However, outcome of the process validation has not been translated to the commercial manufacturing process, and conclusions drawn from the validation batches on the quality control of the IEM should be discussed.

Product specification, analytical procedures, batch analysis

Specifications

The proposed specification is the same as those for Abilify tablets except for the description, identification, IEM activation test and acceptance criteria for dissolution. Accordingly, the specification which is applicable at both release and shelf-life covers main parameters to be tested in solid oral dosage forms.

Discussion on degradation products derived from Aripiprazole is regarded as sufficient. A risk assessment in line with the principles of ICH Q3D has been performed. Amendment of the quality part of the dossier is requested. No risk evaluation on nitrosamine impurities is available yet. Based on current regulatory requirements, a risk evaluation concerning the presence of nitrosamine impurities in the product is required.

Analytical procedures and reference standards

The analytical methods for identification, degradation products/impurities, dissolution and assay were validated according to ICH recommendations. Aripiprazole is very stable and only very little degradation is to be expected at actual storage conditions. Absence of forced degradation study data demonstrating the stability indicating character of assay and related substances methods is thus considered to be negligible. The methodology of the test to determine IEM lifetime has not been sufficiently justified. Validation of the IEM activation test is not seen as appropriate to ensure consistent quality of the finished product**.** It was not shown that the dissolution method is discriminatory (see Pharmaceutical Development).

Information on reference standards is regarded as sufficient.

Batch analysis

Batch data of three batches per tablet strength have been provided for the product in its commercial composition and batch size. It was shown that physico-chemical properties of the tablets are highly reproducible.

Container closure

Aripiprazole + IEM 5 mg, 10 mg, 15 mg and 30 mg tablets are packaged into white, opaque, high density polyethylene (HDPE) bottles, induction heat-sealed, and capped with continuous thread (CT) child-resistant closure with desiccant and coiler. Compliance with Commission Regulation 10/2011 or relevant Ph. Eur. monographs has been confirmed, the relevant information needs to be implemented in the dossier. Submitted information on the packaging material for bulk tablets also has to be included in section 3.2.P.7. Information on the assembled kits (co-packaged non-integral medical devices) needs to be amended with the corresponding specifications. Labelling of the co-packaged devices has been clarified.

Stability of the product

Stability studies of Abilify tablets of all strengths (5 mg, 10 mg, 15 mg and 30 mg) with integrated IEM have been undertaken according to respective ICH recommendations in the commercial packaging. The stability batches have been manufactured in commercial batch size by the proposed finished product manufacturer in the course of process validation. Long-term stability results and accelerated stability results (40°C/75%RH) are available. Under both conditions, all tested parameters were compliant with the proposed specification and no trends were observed. Failure rate of IEM with regards to the

proposed acceptance criteria was very low and not depending on prolonged storage Bulk stability studies were performed with one commercial batch of each tablet strength at 30°C/65%RH Definition of an in-use shelf-life based on adequate stability data is pending as additional data have been requested. Extrapolation beyond the observed range of is not accepted for the proposed drug-device combination. Shelf-life of the finished product will be determined by the functionality of the sensor, and mechanism of degradation of the sensor in the tablet is not known to a sufficient extent. As both acceptance criteria for IEM activation test are questioned, no shelf-life can be granted yet for the finished product.

Post approval change management protocol(s)

Not applicable

Adventitious agents

Lactose monohydrate derived from milk for human consumption is used (BSE statement provided). Magnesium stearate is of plant origin (certificate provided).

GMO

Not applicable

Regional information

Declarations of conformity have been provided for several types the IEM and several types the wearable sensor (patch, pod), which are both class IIa medical devices. In addition, Otsuka Pharmaceutical Europe Limited has provided a declaration of conformity for the Otsuka Medical Software System MyCite App version number 2.0.0, which is a class I medical device. Applicability of the declarations of conformity has been confirmed. The EC certificate number CE 559373 issued by BSI (UK) covers ingestible sensors to signal discrete events and personal monitors for collection of physiological and ingestible sensor signal. Completeness and applicability of the EC certificate has been confirmed.

IEM sensor: the medicinal product and the ingestible device form a single integral product. The requested list of relevant Essential Requirements for the assessment of the safety and performance of the device used with the medicinal product has been provided. However, the information has to be implemented in the quality part of the dossier and some questions are pending**.**

Disclaimer:

The EMA would like to draw the applicant's attention to the utmost importance of ensuring compliance with all applicable EU data protection requirements, in light of the sensitive health data processed by the device to be used in combination with the proposed medicinal product.

The assessment of such compliance falls outside of the scope of the present marketing authorization procedure. The applicant is reminded that the monitoring and enforcement of data protection compliance in this regard is within the remit of the national data protection authorities of Member States.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Drug Substance:

An ASMF for aripiprazole (anhydrous) has been provided

A major objection regarding the acceptability of one of the proposed starting materials has been resolved. The proposed starting material was finally accepted.

As a consequence of above referenced request for redefinition of starting materials, the QP declaration has to be updated to include all intermediate manufacturers from the redefined starting material(s) onwards.

Some 'other concerns' regarding the ASMF AP and RP as well as the drug substance documentation in the MA dossier of the applicant remain to be resolved.

For detailed assessment, please see separate ASMF AR and confidential Annex.

Drug Product:

The drug-device combination product has been defined more clearly in the response of the applicant. Therefore, the respective MO was downgraded to an OC (update of dossier is pending). However, specification of the integral sensor has to be justified, and specifications for the non-integral medical devices are still not available. Based on the information provided, none of the clinical studies filed for marketing authorisation was performed with the patch (strips) and pod version proposed for the commercial product.

The control strategy is not seen as sufficient to guarantee consistent and satisfactory quality and performance of the product with regards to the Ingestible Event Marker (IEM, sensor). **Two MOs** are raised, one concerning the IEM activation test methodology and one concerning the acceptance criteria for the IEM activation test used at release and stability testing.

No risk evaluation on nitrosamine impurities is available yet. Based on current regulatory requirements, a risk evaluation concerning the presence of nitrosamine impurities in the product is required.

As definition of functionality testing is pending, no shelf-life for the finished product can be granted yet. Definition of an in-use shelf life after opening of the bottle has to further justified by stability data.

The Notified Body's evaluation of the benefit-risk determination of the ingestible sensor as medical device is accounted for. A list of the relevant Essential Requirements for the assessment of the safety and performance of the device used with the medicinal product has been submitted. However, the information has to be implemented in the quality part of the dossier and some questions are pending**.**

In addition, numerous OCs regarding the finished product have been identified.

For detailed assessment, please see the Quality Assessment Report.

Overall conclusion:

Four Major Objections regarding the finished product (drug-device combination product) remain. Therefore, both drug substance and finished product documentation are not seen as adequate and sufficient for marketing authorisation.

3.2. Non clinical aspects

3.2.1. Pharmacology

The reference medicinal product (Abilify® tablets 5, 10, 15 and 30 mg) was authorised in the Union on the basis of a complete dossier in accordance with the provisions of the Article 8 of Directive 2001/83/EC (marketing authorisation number EU/1/04/276, date of authorisation 2004-06-04). No new data on the pharmacologically active part of this hybrid were submitted within this application.

Apart from the active substance aripiprazole and the excipients, the use of Abilify MyCite also implies exposure of patients to two medical devices, which require a safety assessment. First, the ingestible sensor, that passes the gastrointestinal tract and might provoke safety concerns. The second medical device is a wearable personal monitor. This plaster-like device is adhesive-backed and needs to be attached to the patient's lower chest via a patch, leading to potential dermal exposure to constituents of the monitor or the patch.

Regarding the ingestible sensor, the applicant provided in 3.2.R an overview of non-clinical studies, which were conducted to obtain a CE marked Class IIa medical device status (i.e., devices with medium risk such as electro-medical devices, which are installed within the body for only between 60 minutes and 30 days) for the sensor.

The applicant conducted studies according to ISO 10993-1: 2009 to gain information on the performance of relevant *in-vitro* and *in-vivo* biocompatibility of the IS. In addition, the applicant was seeking expert guidance from medical device testing laboratories and toxicology consultants to ensure completeness of the biocompatibility programme.

To ensure biocompatibility of the ingestible sensor in Abilify MyCite, theoretical analysis (based upon the materials and their use), *in vitro* chemical and biological characterization, *and in-vivo* biological characterization studies were performed. These early phase studies contained a preliminary chemical characterization and ISO 10993-5 cytotoxicity testing, ISO 10993-11 systemic toxicity testing and ISO 10993-10 irritation testing of the ingestible sensor. Later phase studies contained a canine and rodent oral toxicology study, but also an ingestible sensor copper human health assessment (including quantitative cytotoxicity), and an additional chemical characterization. Finally, mechanical and electrical safety studies were performed to demonstrate that the ingestible sensor does not cause damage to the gastrointestinal lumen.

Apart from the provided non-clinical summary of studies performed for the safety evaluation of the ingestible data, the applicant did not submit any study data nor full protocols in the dossier.

As set out in Annex I to the MDR, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part, together with the relevant general safety and performance requirements (in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council). Both may either be contained in the manufacturer's EU declaration of conformity or in the relevant certificate, issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

As stated further in the Directive 2001/83/EC (Annex I to Directive 2001/83/EC, point 12 of section 3.2): "If the dossier does not include the results of the conformity assessment, and where for the conformity assessment of the device (if used separately), the involvement of a notified body is required in accordance with Regulation (EU) 2017/745), the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and

performance requirements (set out in Annex I to the MDR) issued by a notified body designated in accordance with that Regulation for the type of device in question".

This application includes three medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC, which are required for the intended use of Abilify MyCite. These medical devices and the medicinal product form a single integral product intended exclusively for use in the given combination. The device information on the medical device (aripiprazole + IEM), the EC Certificate (full quality assurance system), and the "declaration of conformity" for both, the Proteus Patch, and the ingestible sensor, were provided by the applicant and are part of the Module 3.2.R.2 (Medical Device) of the dossier. As such, certificates issued by a Notified body (BSI, Notified body number 0086) cover all three devices.

In view of the regulatory framework stated above, a detailed assessment on the safety of the ingestible sensor in Abilify MyCite is not envisaged. The delivered conformity assessment of the ingestible sensor by the responsible notified body is endorsed and in line with the appropriate regulations.

However, there is no indication if the CE marked sensor used for the *in vitro* and *in vivo* studies (biological, electrical and mechanical safety studies) included and described in the CE-marking technical file, is the same type of sensor as used in the clinical trials, and the same final ingestible sensor version as intended for approval. The applicant should clarify, if the sensor tested in the studies described in the non-clinical part of the dossier (CE certificate/registration number 559373) is the same as that used in the clinical studies.

3.2.2. Pharmacokinetics

The pharmacokinetic profile of aripiprazole after oral administration has been thoroughly studied and discussed in previous submissions (EMEA-H-C-000471 and EMEA/H/C/000471/R/0059). No new pharmacokinetic studies have been performed and provided with this hybrid application, which is acceptable.

3.2.3. Toxicology

The non-clinical safety profile of orally administered aripiprazole has been adequately characterized in the Marketing Authorization Application (MAA) for Abilify® (EMEA-H-C-000471).

No new internal non-clinical toxicology studies supporting the oral route of administration and the registration of Abilify MyCite, have been generated for Abilify since the 5-year renewal was submitted in October 2008 (EMEA/H/C/000471/R/0059)

Furthermore, the safety and efficacy of Abilify MyCite in children and adolescents from 0 through 17 years of age have not been established.

3.2.4. Ecotoxicity/environmental risk assessment

A complete environmental risk assessment (Phase II Tier A and Tier B) report has been submitted on Abilify using the worst case scenario for the market penetration factor (Fpen = 0.01) and a maximum daily dose of 30 mg.

As a result of the above considerations on aripiprazole, the available data allow to conclude on the absence of a potential risk of Abilify MyCite to the environment.

The IEM is regarded as an integrated medical device and as such, there is no requirement of an environmental risk assessment for the sensor.

3.2.5. Discussion on non-clinical aspects

Abilify MyCite is a drug-device combination product comprised of an aripiprazole tablet embedded with an ingestible sensor to measure medication intake that is registered with a compatible personal monitor. The active substance in Abilify MyCite, aripiprazole, falls into the pharmacotherapeutic group of psycholeptics and other antipsychotics (ATC code N05AX12).

As this is a hybrid application, certain documents in Modules 4 and 5 are not required and thus were not included in the eCTD. In line with the legal basis, the applicant did not submit any relevant new non-clinical data for the active substance aripiprazole.

A review of non-clinical information published for aripiprazole after the 5-year MAA renewal in 2008 (EMEA/H/C/000471/R/0059) was conducted and brief summaries of relevant references were included. No Company-sponsored non-clinical studies related to the primary effects of aripiprazole have been conducted; available publications were submitted.

To facilitate the development of the sensor and to help validate its safety and technical performance, the applicant has performed a series of computer simulations, benchtop testing, and *in-vitro* as well as *in-vivo* non-clinical studies.

The applicant declared that the CE marked products falling within Class IIa meet the provisions of the applicable EC-Directive (93/42/EEC, as amended by 2007/47/EC).

No definite study results of the ingestible sensor have been provided in the dossier; however, details of the non-clinical studies were included within the CE-marking technical file. This is considered appropriate and in line with the medical device regulation (MDR 2017/745).

Medical devices may be placed on the market and/or put into service in the EEA only if they comply with the requirements laid down in the relevant European Directive (s) and after an appropriate conformity assessment procedure has been performed, a corresponding declaration of conformity has been issued and the CE marking has been affixed. The appropriate "Declarations of Conformity" were indeed provided by the applicant for each medical device.

The non-clinical pharmacokinetic, toxicity and safety profile of orally administered aripiprazole has been characterized previously in the Marketing Authorization Application (MAA) for Abilify® (EMEA-H-C-000471). The majority of these studies were performed in dogs, but also in pigs, and included testing of both the patch and the ingestible sensor. Only a fraction of the available data was presented in the dossier. However, it is expected that the Notified bodies critically evaluated all studies during the CE-marking procedure. No additional non-clinical studies were conducted by Otsuka to support the registration of Abilify MyCite.

3.2.6. Conclusion on non-clinical aspects

Overall, from a non-clinical perspective, there are no objections to a marketing approval of this hybrid application, according to Regulation (EC) No 726/2004, as long as the pending issue on the sensor can be resolved.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Table 2

Study ID/ Study period	**No. of study centres / locations**	**Design/ Duration**	**Study Posology**	**Study Objective(s)**	**Subjects enrolled/ treated/ completed**	**Gender Mean Age Mean BMI**	**Diagnosis Incl. criteria**	**Primary endpoint**
316-14-220 27 Aug 2014 - 07 Jul 2015	6 sites/ USA	Phase IIa, open-label, multicentre, single-arm, therapeutic, exploratory Duration: 8 weeks	MIND 1 system: aripiprazole (10, 15, 20, or 30 mg) plus the embedded IEM and related patch and app	Primary Objective: To measure the usability of the MIND1 System by adult subjects with schizophrenia, with regard to the ability to pair and apply the patch independently and successfully by the end of the Week 8 trial visit. Secondary Objectives: - To measure the usability of the MIND1 System by adult subjects with schizophrenia, with regard to the ability to pair and apply the patch successfully by the end of the Week 8 trial visit, independently or with minimum assistance; - To measure the usability of the MIND1 System by adult subjects with schizophrenia, with regard to the ability to wear the	In total: 67/67/49 Cohort 1: 37/37/27 Cohort 2: 30/30/22	In total: 46.6 years Cohort 1: 45.8 years Cohort 2: 47.6 years In total: 31.9 kg/m^2 Cohort 1: 31.2 kg/m^2 Cohort 2: 32.6 kg/m^2	Adult (18-65 years) subjects with schizophrenia who had been prescribed and stabilized on oral aripiprazole at the time of screening	The proportion of subjects who were able to pair and apply a patch independently and successfully by the end of the Week 8 trial visit (or early termination if applicable), as defined as a score of 91 to 100 on the Subject Ability to Use System Scale - Healthcare Professional Version (SAUSS-HCP).

				patch regularly. - Safety				
316-13-215 08 Mar 2016 - 08 Sep 2016	4 sites/ USA	Phase II, open-label, multicenter, single-arm, therapeutic, exploratory Duration: 8 weeks	DMS: Daily oral prescribed aripiprazole (2, 5, 10, 15, 20, or 30 mg) + IEM to be used together with the related patch and app	Primary objective: To assess the functionality of an integrated call center for DMS by adult subjects with schizophrenia (SCH), major depressive disorder (MDD), or bipolar 1 disorder (BP1) who were treated with oral aripiprazole. Exploratory objective: To explore the use of DMS as measured by patch wear time, subject and HCP engagement, and subject satisfaction with the system. Safety	49/49/38	46.4 years 35.9 kg/m^2	Adult subjects (age 18-65 years) with SCH, MDD, or BP1 who were receiving a stable single daily oral dose of prescribed aripiprazole (2, 5, 10, 15, 20, or 30 mg)	The establishment of a functional and operational integrated call center with coordinated feedback to the subject and investigative site to optimize the use of DMS as measured by: - Inbound calls (i.e., calls from the subject to the integrated call center) by help type; - Outbound calls (i.e., calls from the integrated call center to the subject) by help type.

BMI= Body Mass Index; BP1=bipolar 1 disorder; MDD= major depressive disorder; IEM= ingestible event marker; HCP= health care provider; SCH= schizophrenia; DMS=Digital Medicine System (DMS), MIND 1 system; both are previous names of the Abilify MyCite system

The versions of the components used in study 316-14-220 were:

Cohort 1: version IEM and Patch (RP4) combination, with the Otsuka Medical Software Version 1.4; Cohort 2: version IEM and Patch (DW5) combination, with the Otsuka Medical Software Version 1.5.

The versions of the components used in study 316-13-215 were:

IEM and DW5 patch combination (/DW5) with the DMS software application Version 1.5.3.

3.3.1. Pharmacology

No new pharmacokinetic (PK), pharmacodynamic (PD) or PK/PD studies were conducted.

The pharmacokinetics (PK) and pharmacodynamics (PD) of aripiprazole administered as an oral tablet to adults have been defined within the Marketing Authorisation Application for Abilify® (EMEA/H/C/000471).

- **Bioequivalence**

Description and Dosage Form

Aripiprazole + IEM tablets are developed as drug-device combination product in 5-, 10-, 15-, and 30-mg strengths and are packaged in high-density polyethylene (HDPE) bottles with desiccant.

The shapes and sizes of the Abilify tablets with and without sensor are the same. Concerning the qualitative and quantitative composition, the only difference between both products is the slightly different amount of and Whereas the colouring agents remain the same, the colour amounts were in the Abilify MyCite tablets in order to allow distinguishing them from the Abilify tablets without sensor. Upon request of the Rapporteurs, the applicant provided a visual comparison between both products, which shows that the tablets actually are easily distinguishable. The likelihood of mix-up between Abilify tablets with and without sensor is further reduced as both products are packed differently (bottles vs blisters).

In vitro dissolution

The proposed aripiprazole + IEM tablets are manufactured by compressing Abilify (aripiprazole) granulations with IEM. The major difference between aripiprazole + IEM tablets and commercial Abilify® tablets is the presence of an IEM embedded in the Abilify MyCite tablet.

Once ingested, the aripiprazole + IEM tablet disintegrates, releasing aripiprazole and the IEM from the tablet. The presence and release of the IEM occurs without having any effect on the release characteristics of the tablet, and *vice versa*. Subsequently, the IEM and aripiprazole work separately and independently in the body without any interaction between them. To examine whether the two components of the aripiprazole + IEM tablet behave physiologically and physico-chemically independent of each other, two tablet in vitro dissolution tests and IEM activation tests were conducted.

The first *in vitro* dissolution testing is not considered supportive for the present MAA as tests were performed with Abilify MyCite tablets not intended for commercialisation. For the to-be-marketed products, the tablet composition has been changed) in order to differentiate between Abilify tablets with and without IEM.

The second *in vitro* dissolution testing was performed with commercial Abilify MyCite tablets with reduced colorant. However, a thorough description of the experimental settings and analytical methods including validation data is still missing and several other deficiencies were identified.

Thus, from the data provided on the *in vitro* dissolution tests, no conclusions on bioequivalence between the test and reference product can be made at present; the bridge to the reference product remains thus questionable.

IEM activation

Apparently, in the course of the development programme of the Proteus system. According to the applicant, the IEM is the sensor which will be used in the to be marketed Abilify MyCite tablets. Both and IEMs were reported to have exactly the same. It was noted however, that no detailed description

of both IEMs with regard to their composition and measures has been provided by the applicant in the original submission. Upon request of the Rapporteurs the applicant submitted such. Tests were developed and conducted to measure the presence and functionality of the IEM within the aripiprazole tablets.

Considering both, safety and efficacy, not only a proper function of the IEM is crucial for the overall functionality of the Abilify MyCite system, but also its range of signal (in cm), which is needed for a positive detection by the patch. In the original submission as well as upon request of the Rapporteurs, no information was provided by the applicant on the exact range [in cm] of the signal of the IEM and on what range is necessary for a positive detection by the patch. These issues thus remain unresolved.

- **Influence of food**

In the "Proteus Ingestible Sensor Safety Summary" (in Module 3.2.R of the dossier), a short paragraph concerning "food and IS co-ingestion" is provided. Herein it is stated, that a clinical study has demonstrated that food and beverages including alcohol do not affect IS function in any clinically significant manner. It remained however, unknown which clinical studies are referred to as no details at all have been provided in the original submission (not even the study titles) and what drug-device system was investigated (IEM combined with aripiprazole, and if yes, was it the to be marketed Abilify MyCite system?).

Hence, the conclusion of the applicant "that food and beverages including alcohol do not affect IS function in any clinically significant manner" could not be verified at all. The respective recommendation proposed in the PI, that Abilify MyCite can be taken "with or without food" could therefore also not be supported. The applicant was thus asked to submit the clinical studies referred to and to further discuss their results and their applicability for the to-be commercialized Abilify MyCite system.

The applicant responded very briefly, that altogether 4 *in vitro* and *in vivo* studies were conducted to demonstrate the absence of any food/drink/alcohol effect on the IEM. No discussion at all or adequate presentation of their results was provided as requested. The 4 studies were only added to the "List of References" and the study reports were submitted. The applicability of the results of these studies to the Abilify MyCite system to be marketed was also not addressed. Hence, the concern raised remains unresolved.

- **Excretion**

The excretion of aripiprazole has been assessed previously in the MAA for Abilify® and is sufficiently described in the proposed SmPC. However, the applicant does not provide any clinical data on the excretion of the IEM. Although it is stated that safety tests in a canine model indicated that the IEM was excreted reliably and did not cause mechanical injury to the lumen of the gastrointestinal tract, it is not entirely clear on which data this conclusion is based and what the term "excreted reliably" means in this regard. In the submitted clinical studies, patients were not monitored for the excretion of the IEM. In human pathological conditions such as diverticulosis, IEM deposition could lead to inflammation and perforation of diverticula, ultimately requiring surgery. This remains an uncertainty in the use of the product.

3.3.2. Discussion on clinical pharmacology

No new clinical pharmacology information was provided with this submission. For demonstration of bioequivalence with the reference product Abilify, comparative *in vitro* dissolution studies were conducted. This is an acceptable approach for a hybrid application. However, several deficiencies were

identified with regard to the conducted ***in vitro* dissolution** testing which remain to be resolved by the applicant (see List of outstanding issues). Thus, no conclusion on the overall comparability between the applied- and the reference product is presently possible, i.e. the bridge to the reference product remains questionable.

From a clinical perspective, considering both, safety and efficacy, proper function of the IEM is crucial for the overall functionality of the Abilify MyCite system. If the lifetime of the IEM is zero, no pill intake will be recorded leading to false-negative results and potential intake of an extra dose. If the lifetime of the IEM is too short (below 49 seconds), the patch will not detect the signal either. With this regard, the concerns raised have not been resolved. In this context, also the IEM´s signal range (in cm) needed for a positive detection by the patch is considered essential. The applicant did not provide any information concerning this issue, which thus also remains unresolved.

The applicant´s conclusion that "**food** and beverages including alcohol do not affect IS function in any clinically significant manner" cannot be verified as the results of the studies referred to have neither been presented nor discussed adequately. The respective recommendation in the PI, i.e. that Abilify MyCite can be taken "with or without food," remains therefore currently also not supported.

The applicant does not provide any reliable clinical data which allow drawing firm conclusions concerning the **excretion of the IEM** in humans. Although it is stated that safety tests in a canine model indicated that the IEM was reliably excreted and did not cause mechanical injury to the lumen of the gastrointestinal tract, it is not entirely clear on which data this conclusion is based on and what the term "excreted reliably" means in this regard. In the submitted clinical studies, patients were not monitored for the excretion of the IEM. In humans with diverticulosis, a diverticulum might be a potential depot for the IEM. Deposition could lead to inflammation and perforation of the diverticulum, ultimately requiring surgery. This remains an uncertainty in the use of the product.

3.3.3. Conclusions on clinical pharmacology

Presently, no conclusions on the comparability between Abilify MyCite and its reference product Abilify (which serves as the legal basis for this "hybrid application") can be drawn based on the *in vitro* dissolution testings provided, and the bridge to the reference product thus remains questioned.

Based on the *in vitro* IEM activation testing performed, several concerns arose and still remain unresolved with regard to the proper functionality of the IEM and in consequence of the whole Abilify MyCite system.

These concerns need to be addressed before final conclusions on the bioequivalence as well as on the overall functionality of the drug-device system can be made.

3.3.4. Clinical efficacy

Dose-response studies

Not applicable.

Main studies

No clinical trials using standard measures of efficacy have been performed with the drug-device combination. The main clinical studies submitted in this application are two open label, single-arm, multicentre, therapeutic exploratory trials, **study 316-14-220** and **study 316-13-215**.

Study 316-14-220

Study 316-14-220 was an 8-week, open label, single-arm, multicentre trial assessing the usability (in particular of the patch) of the Abilify MyCite system (then referred to as MIND1 system) in adult patients with schizophrenia who were treated with oral aripiprazole. The trial period was from August 27th 2014 to December 3rd 2014 (Cohort 1) / July 7th 2015 (Cohort 2).

Methodology

A total of 67 subjects were included at 6 trial sites in the US. The subjects were divided into two Cohorts, as during trial conduct a new version of the MIND 1 system was introduced (Protocol Amendment 1). Subjects enrolled under the original version of the protocol were considered to comprise a first cohort (Cohort 1), while subjects enrolled under Protocol Amendment 1 were considered to comprise a separate second cohort (Cohort 2). Each cohort included only one treatment group; there was no control group. Cohort 1 comprised 37 subjects and Cohort 2 comprised 30 subjects.

For each of the 2 cohorts, approximately 32 subjects were planned to be enrolled at 6 trial sites in the US, for a total of 64 subjects. At the end, this trial was conducted in a total of 67 subjects (37 subjects in Cohort 1, 30 subjects in Cohort 2) at 6 trial sites in the United States (US).

The two different versions of the MIND 1 system that were utilised in study 316-14-220 are shown in Table 3:

Table 3: MIND1 Component Versions used in Trial 316-14-220 in Cohorts 1 and 2.

MIND1 Component Versions in Trial 316-14-220				
			Otsuka Medical Software	
Cohort	**IEM**	**Proteus Patch**	**Patient Component (app)**	**Healthcare Provider Web Portal**
Cohort 1		RP4	v1.4.5	v1.4
Cohort 2		DW5	V1.5.2	v1.5

Note: The Caregiver Web Portal was not used in Trial 316-14-220; Source: Table 9.1-1, CSR Study 316-14-220

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 3-week training phase during the first part of the treatment period and then a 5-week independent phase during the second part of the treatment period.

During the training phase of the treatment period, subjects received direct training by trial site staff at each of the scheduled trial visits (i.e., baseline and Weeks 1, 2, and 3). During the independent phase, the subject was required to change the patch (remove the previous patch, ensuring all data from that patch had been uploaded, and then pair and apply the next patch) independently (and/or with the assistance of a caregiver/support person, if applicable) once weekly until returning to the trial site for the Week 8 visit.

During the treatment period of this trial, all subjects took aripiprazole + IEM tablets; subjects were to be maintained throughout the trial on the same prescribed dose and regimen of aripiprazole that they

were taking at the time of the screening visit (10, 15, 20, or 30 mg, once daily) as feasible and clinically indicated. In addition, placebo + IEM tablets were used for training purposes only during defined scheduled trial site visits.

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.

Study Amendments

The study protocol was amended once (please refer to the Clinical AR for details). The major amendment to the protocol of trial 316-14-220 occurred when the trial was already well under way and when a different version of the MIND 1 system was introduced (Table 1 above). The protocol changes resulted also in a slightly bigger sample size, in a modification of the primary endpoint and in the addition of a secondary endpoint ("To measure the usability of the MIND1 System by adult subjects with schizophrenia, with regard to the ability to pair and apply the patch successfully by the end of the Week 8 study visit, independently or with minimum assistance."). The primary endpoint text was modified as follows: an independent and successful pairing and applying of the patch was "... defined as a score of 91 to 100 on ... (SAUSS-HCP)".

Protocol deviations

In addition to the protocol amendments, also several protocol deviations occurred, in both cohorts and in all 6 trial sites, respectively (please refer to the Clinical AR for details). The deviations concerned in particular dosing errors (e.g. missed doses, overdosing) and procedural deviations (affecting the primary outcome variables), many of those affecting the patch; e.g. patch fell off or was removed and no new patch was applied, patch was not worn, patch was not paired.

Changes in Planned Analyses

The following objectives were not assessed because the relevant technology to generate usage duration data for those endpoints was not yet available:

- To assess the engagement of subjects during the study by measuring the proportion of time they are using the software application;
- To assess the frequency that site staff accesses the healthcare professional portal.

In addition, the following other objective was not assessed due to the low number of caregivers/ support persons in Cohort 1 and the absence of caregivers/support persons in Cohort 2:

- For subjects with caregivers/support persons, to assess how much support the subject needed from caregiver/support person during the training and independent phases until the subject was able to pair and apply the patch independently and successfully, as measured by a questionnaire scale.

Study participants

Inclusion and exclusion

Only subjects who were *cooperative,* who *were able to ingest oral medication* and *who were willing to adhere* to the trial requirements and thus to study treatment were enrolled. In addition, only subjects were included who were currently prescribed oral aripiprazole for schizophrenia (10, 15, 20, or 30 mg once daily), and who were deemed likely to *remain on this same stable* dose and for whom *no dose adjustments were considered necessary* anymore.

Demographics and baseline characteristics

Demographic and baseline characteristics were generally similar across the 2 cohorts. An imbalance with regard to gender (more male than female subjects) and ethnicity is however, noticed. Overall, the mean age of subjects was 46.6 years and their mean BMI was 31.9 kg/m2.

Patients included had a diagnosis of schizophrenia (2.2 - 38.2 years before enrollment; mean: 19.3 years); the level of impairment was relatively low (subjects with a current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder were excluded). The majority (70.1%) of the participants was rated as "mildly ill" on the CGI-S scale and patients had to be capable of using a smartphone. In addition, all patients were on a stable dose of aripiprazole before trial conduct

The majority of the study participants (55/67 subjects) reportedly took concomitant medications during the trial, including psycholeptics and psychoanaleptics.

Treatments administered

Study 316-14-220 was conducted from 27 Aug 2014 to 03 Dec 2014 (Cohort 1) / 07 Jul 2015 (Cohort 2). As outlined above (Table 1) two different versions of the Abilify MyCite system (then called MIND 1 system), which concerned in particular the Patch and the Otsuka Medical Software used in the trial. The differences between these two systems were not described and potential differences between these two systems and the to-be marketed one are also unknown.

During the treatment period, all subjects took aripiprazole (10, 15, 20 or 30 mg) plus IEM tablets (at their prescribed aripiprazole dose). Subjects were to ingest one tablet per day with 4 ounces of water. In addition, placebo + IEM tablets were used for training purposes only during defined scheduled trial site visits.

At the baseline visit (i.e., Day 1 of the treatment period), subjects discontinued their normally prescribed oral aripiprazole tablets and began taking the aripiprazole + IEM tablets at the previously prescribed dose for the 8-week treatment period. Upon completion of the treatment period subjects resumed their normally prescribed oral aripiprazole treatment.

The patch is an un-medicated adhesive device worn on the torso and designed for 7-day wear. The function of the patch is to detect and time-stamp each IEM ingestion, and measure and record other date- and time-stamped physiologic and behavioural data, such as heart rate and levels of physical activity and rest.

A commercially available mobile computing device (i.e., smartphone) and accessories were dispensed to subjects for use during participation in the trial. Basic usage and maintenance instructions were given. The smartphone was to be charged daily (however, if the smartphone battery became fully depleted, the MIND1 data were not lost, as the data would remain stored on the patch). Subjects were requested to carry the trial smartphone with them as much as possible and to plug in the device at a dedicated location at home when it was not being carried.

The subject was able to view his/her selected data at will on the smartphone. The MIND1 data were also viewable on the healthcare professional portal provided only to trial staff identified before start of trial.

All patients were trained for 3 weeks before they were left 5 weeks alone to use the system correctly, and during a subject's participation in the trial, a call centre and trial site staff were available for assistance.

Identity of Investigational Product(s)

The aripiprazole + IEM and placebo + IEM tablets were provided by the sponsor, the patches were provided by Proteus Digital Health, and the commercially available mobile computing device (i.e., smartphone) were provided by Verizon and AT&T. The sponsor had operating procedures in place to ensure the suitability of the trial-related IMP provided to the trial sites.

Each container of MIND1 IMP (aripiprazole + IEM) was labelled to clearly disclose important identifying information (e.g., trial number, sponsor name and address, instructions for use, route of administration, appropriate precautionary statements, other information required by local regulatory authorities).

Certificates of analysis are provided and a list of by-subject drug lot numbers for aripiprazole + IEM and placebo + IEM are appended to the report. No batch numbers of the drug-device products used in the study were provided.

Objectives

The primary objective of Study 316-14-220 was to measure the usability of the MIND1 system by adult subjects with schizophrenia, with regard to the ability to pair and apply the patch independently and successfully by the end of the Week 8 trial visit.

The key secondary objective was to measure the usability of the MIND1 System by adult subjects with schizophrenia, with regard to the ability to pair and apply the patch successfully by the end of the Week 8 trial visit, independently or with minimum assistance.
Another secondary objective was to measure the usability of the MIND1 System by adult subjects with schizophrenia, with regard to the ability to wear the patch regularly.

Endpoints

The **primary endpoint** of this trial was the proportion of subjects who were able to pair and apply a patch independently and successfully by the end of the Week 8 trial visit (or early termination if applicable), as defined as a score of 91 to 100 on the Subject Ability to Use System Scale - Healthcare Professional Version (SAUSS-HCP).

The SAUSS-HCP score was developed by the applicant for study 316-14-220 to assess the primary and key secondary endpoints.

The **secondary endpoints** were:

- Proportion of subjects who were able to pair and apply a patch successfully by the end of the Week 8 trial visit (or early termination if applicable) independently or with minimum assistance, as defined by a SAUSS-HCP score of 71 to 100;
- Proportion of time during the trial period when subjects wore their patches; the time duration of patch wearing was calculated based on digital health data.

Other exploratory endpoints were:

- The time to the first occurrence of the subject being able to pair and apply the patch independently and successfully;
- The support level the subject needed from a caregiver/support person, as applicable, as assessed using a Caregiver/Support Person Involvement Scale;*
- Levels of satisfaction as measured by a Subject Satisfaction Scale;

- Perceived usability as measured by a Healthcare Professional Usability Assessment Scale and a Subject Usability Scale, as well as a Caregiver/Support Person Involvement Scale (as applicable*);
- The proportion of days subjects used the application and the proportion of days investigators and/or other trial site staff used the healthcare professional portal during the trial;**
- The frequency of Call Center support by help type;
- The proportion of ingested IEMs registered on digital health data server versus expected IEMs ingested;
- Clinical Global Impression – Severity scale (CGI-S)
- Clinical Global Impression – Improvement scale (CGI-I)
- Patient Global Impression – Improvement scale (PGI-I)
- Positive and Negative Syndrome Scale (PANSS)

*This endpoint was not assessed due to the low number of caregivers/support persons in Cohort 1 and the absence of caregivers/support persons in Cohort 2.
**This endpoint was not assessed because the relevant technology to generate usage duration data was not yet available, as noted in Section "Changes in Planned Analyses".

For a detailed description of the above described scales please refer to the Clinical AR.

Statistical Methods

Sample size

Sample size was planned aiming at the width of the confidence interval. Approximately 32 subjects were to be enrolled to produce a 2-sided 95% CI with a width of 0.298 and a lower limit of 0.621 for the proportion of subjects who were able to pair and apply a patch independently and successfully when the sample proportion was 0.8, in each of Cohorts 1 and 2, for a total of 64 subjects. Corresponding computations can be reproduced. The underlying assumption (sample proportion of 0.8) and the clinical relevance of the targeted width are not discussed. Targeting the width of the confidence interval imposes no restrictions in terms of the lower bound of the confidence interval. Sample size considerations indicate that demonstration of a proportion of subjects independently able to place/pair the patch above 60% was targeted. The exact Clopper-Pearson method was used in the sample size calculation, which was based on the binomial distribution.

The primary objective of this study was the estimate the proportion and corresponding confidence interval of subjects who were independently able to place/pair the patch according to SAUSS-HCP score. No statistical hypotheses were specified for either endpoint. Study protocol versions preceding Amendment 1 were not provided by the applicant. It is unclear how the original sample size calculation could have anticipated inclusion of a second cohort.

Numbers analysed

In both Cohorts, 71 subjects were screened, 67 were enrolled and treated with the MIND1 system. Out of the 67 subjects included in the trial, 49 completed the 8-week treatment period (73.1%). The ITT population consisted of 67 subjects. All subjects were analysed for efficacy and safety.

The primary objective of this study was the estimate the proportion and corresponding confidence interval of subjects who were independently able to place/pair the patch at at least one study visit according to SAUSS-HCP score. No statistical hypotheses were specified for either endpoint. Sample

size considerations indicate that demonstration of a proportion of subjects independently able to place/pair the patch above 60% was targeted.

Missing data:

For the primary endpoint analysis, subject with missing end of treatment assessment were considered failures. For the analysis of change from baseline, last-observation-carried-forward was foreseen.

Worst-case imputation of the primary endpoint is considered acceptable. LOCF requires assumptions about the outcome distribution that are typically not considered plausible. Considering that only exploratory endpoints are affected no concern is raised at the moment.

Analysis sets

Both the Safety and ITT Sample require that subjects used the MIND1 System. This is not considered adequate as subjects who e.g. could still refuse treatment once enrolled would not be represented in the safety and efficacy analysis. Considering however, that all enrolled subjects were included in the ITT and Safety Sample, no concern is raised.

Primary efficacy analysis

The estimate of the proportion of subjects with SAUSS-HCP scores above 90 and its 95% confidence interval was planned to be computed using exact Clopper-Pearson Binomial method by cohort. Use of the Clopper-Pearson provides coverage probabilities that are equal or larger than nominal levels, which is considered appropriate for the estimation of proportions.

Secondary efficacy analysis

Analysis of the proportion of subjects with scores above 70 was performed using the Clopper-Pearson method as well, that is supported. Analysis of wear time was performed by computing the ratio of actual patch wear time to total expected patch wear time. Actual patch wear time was estimated by the time difference between pairing of the patch and time of the last step recorded by the device. It is not clear how total expected patch wear time was computed. It is assumed though that this corresponds to the time the subject should have worn a patch. Patch wear time was analysed using descriptive statistics. Consequently, extrapolation of results to the target population is not supported.

Interim analyses

It is unclear whether results from the interim analysis may have resulted in modifications of the study design/conduct for the second cohort. Consequently, results obtained from data pooled across cohorts may be subject to estimation bias, nominal coverage probabilities of corresponding confidence intervals may be inflated.

Randomisation and blinding (masking)

As this was an uncontrolled, open-label study, no comparator/control group and no randomisation were carried out. No blinding was foreseen in this uncontrolled trial and neither patients nor treating physicians or other staff members were blinded.

Results

The trial was conducted at 6 sites in the US. Overall, 67 subjects were enrolled of whom 49 (73.1%) completed the study.

18/67 subjects (26.9%) discontinued, mainly due to withdrawal of consent to participate (6 subjects; 9%) and AEs (6 subjects; 9%). Most of the AEs leading to discontinuation were TEAEs and associated

to the Patch (rash, rash papular, pruritus, skin discolouration, and rash pruritic) (please refer to Section 3.3.7 "Clinical Safety").

All enrolled subjects were included in the efficacy and safety analyses.

Outcomes and estimation

Primary endpoint

Overall, 37 of 67 (55.2%) subjects were **able to pair and apply a patch independently and successfully by Week 8** (95% CI, 42.6%, 67.4%) as defined as **a score of 91 to 100 on the SAUSS-HCP**.

Results varied across sites (from 26.7% to 73.3%) but were similar between Cohorts 1 and 2. The by-week analysis indicated that the proportion of subjects able to pair and apply a patch independently and successfully consistently increased from baseline though Week 8.

The treatment period lasted 8 weeks. The primary endpoint was defined as the proportion of subjects who were able to pair and apply a patch independently and successfully by the end of the Week 8 trial visit (or early termination if applicable), which was evaluated using the SAUSS-HCP. If the subject's score was between 91 and 100, inclusive, for a particular visit, the subject was considered a success at that visit (otherwise, the subject was considered a failure at that visit). A subject who was rated as a success for at least one post baseline visit (including Weeks 1, 2, 3, and 8/early termination) was considered to be able to pair and apply a patch independently and successfully by the Week 8 or early termination visit.

Secondary endpoints

The main secondary endpoint was the **proportion of patients who were able to pair and apply the patch independently or with minimal assistance by Week 8 as defined by the SAUSS-HCP score of 71 to 100.**

According to the results provided, 55 out of 67 patients (82.1%) achieved this secondary endpoint. Results were similar across Cohorts 1 and 2.

The other secondary endpoint "**Ability to wear the patch regularly**" revealed that the subjects of both cohorts wore the patch for a mean (SD) of 70.7% (24.7%) of the trial period. Although mean patch wearing time was somewhat longer for Cohort 1 versus Cohort 2 (74.4% vs 66.2%, respectively), median values for across cohorts were similar (78.4% vs 77.1%, respectively).

Overall, the 67 subjects used a mean (SD) of 9.6 (4.4) patches during the trial. The average time each of the subjects wore their patches was a mean (SD) of 3.6 (1.6) days and the median wearing time was a mean (SD) of 3.5 (2.1) days. Similarly, for all of the 626 patches worn during the trial, the average wearing time per patch was a mean (SD) of 3.6 (2.7) days.

Other Efficacy Analyses

Another exploratory objective was **the time to first occurrence of a subject being able to pair and apply the patch independently and successfully**. The median time to first occurrence of a subject being able to pair and apply the patch independently and successfully was 29.0 days overall, and 29.0 days and 23.0 days for Cohorts 1 and 2, respectively.

For all questions on the **Subject Satisfaction Scale,** at Week 8, 53 subjects responded and answered that the MIND1 System was „somewhat easy (22.6%), easy (34%), or extremely easy (9.4%) to use".

In management of their condition 53 subjects responded that it was „somewhat helpful (20.6%), helpful (28.2%), or extremely helpful (18.9%)"; in improving discussions with their doctor (and others in the treatment team) 13.2% found it was „somewhat helpful, 45.3% found it helpful, 20.8% found it „extremely helpful". At Week 8, approximately 53 subjects responded. Of these 15.1%) were „somewhat satisfied, 45.3% were satisfied, 20.8% were extremely satisfied" with the system. Approximately 18.8% would be „somewhat likely, 26.4% would be „likely", 22.6% would be extremely likely" to use it in the future (if available and recommended by their doctor).

The **Healthcare Professional Satisfaction Scale** (only performed for Cohort 1) was answered by 6 HCPs, of those 4 were "satisfied" with the MIND 1 system.

HCPs that responded on the **Healthcare Professional Usability Scale** found that it was "easy (53.3%) or extremely easy (28.3%)" to apply the patch for themselves and for their patients (58.3% or 20%, respectively). For activities involving the app, HCPs responded that it easy (38.3%) or extremely easy (11.7%) to pair the patch with the app and easy (51.7%) or extremely easy (20%) to use the app. In the HCPs' opinion, activities involving the app were somewhat less easy for the subjects: pairing of the patch with the app was found easy for 20% or extremely easy for 5% of the subjects and use of the app was easy for 38.3% or extremely easy for 10% of subjects.

The HCPs responded that use of the whole MIND1 System (patch, pills, and app) was easy (40%) or extremely easy (20%) for ~52% of the HCPs and ~35% of the subjects (38.3% or 10%, respectively).

In their overall assessment with the MIND1 System, a majority of HCPs was satisfied (55%; none were extremely satisfied). Furthermore, the responses to questions indicated that the HCPs generally viewed the system to be helpful for themselves and for their patient, although there were a few exceptions (e.g., for Question 7, a majority [53.3%] of HCPs was neutral on whether the system helped to adjust clinical decisions by providing additional information).

Using the **Subject Usability Scale**, by the last visit, subjects most frequently responded that applying the patch was easy (37.1%) or extremely easy (35.5%); pairing the patch was easy (25.8%) or somewhat easy (25.8%); and using the app was easy (43.5%) or extremely easy (19.4%).

At the last visit, 37.1% of subjects reported that they had required assistance (since their previous visit) when changing and pairing patches. Of subjects requiring assistance, assistance with applying the patch was less frequently required (51.9% of subjects never required help) and assistance with pairing the patch to the app was most frequently required a few times per month (40.7%).

Frequency of **Call Center support** was summarized by help type and visit. Total Call Center help at Week 1 was required by 39 of 65 (60.0%) subjects and was lower for subsequent weeks (Week 2, 33 of 63 [52.4%] subjects; Week 3, 26 of 63 [41.3%] subjects; Weeks 4/5, 31 of 58 [53.4%] subjects; Weeks 6/7, 20 of 51 [39.2%] subjects). For each week, the most frequent category requiring Call Center help was the app.

According to the applicant, the **proportion of ingested (vs expected) aripiprazole + IEM tablets reflects the subjects' daily use of the system**. To conclude, if a subject uses the system correctly, the detection accuracy of the subject´s ingested IEMs should be 100%.

However, the proportion of ingested aripiprazole + IEM tablets as registered on the digital health data server (vs expected ingestions) was only 59.4% (1824/3072) across all expected ingestion days during the trial. It is further noticeable, that, in total, also only 93.2% of the IEMs of the placebo+IEM tablets (which the patients took under supervision of the trial stuff) were registered.

In addition, the mean CGI-S scores, CGI-I scores, PGI-I scores and PANSS total scores were assessed over the course of the study. Overall, these scores revealing no clinically relevant changes.

Ancillary analyses

N/A

Trial 316-13-215

Methods

This was an open-label, single-arm trial designed to **assess the functionality of an integrated call center** for DMS as used by adult subjects with SCH, BP1, or MDD being treated with oral aripiprazole. A schematic of the trial design is represented in the Figure 3 below.

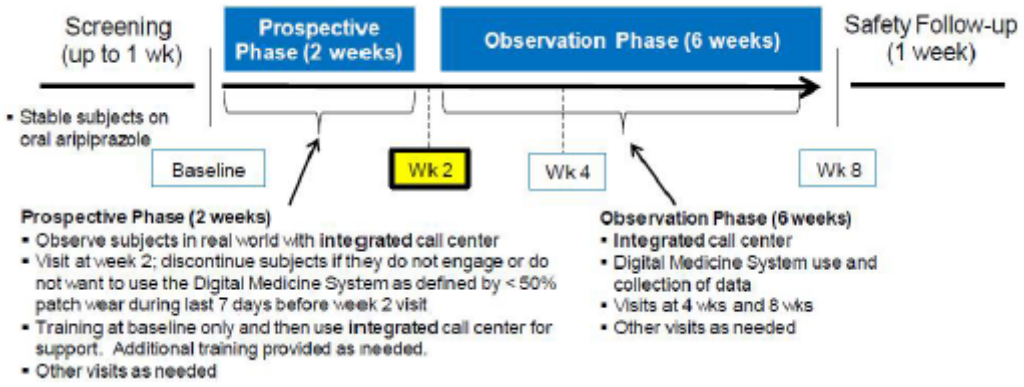


Figure 3: Trial Design Schematic

The study was divided into three phases: screening, assessment and follow-up phase. Furthermore, the assessment phase was separated into a two-week prospective phase and a 6-week observation phase. Only subjects who demonstrated adherence with the system (defined as ≥ 50% patch wear time during the last 7 days before the Week 2 visit), were allowed to continue into the 6-week observation phase.

Study Participants

Subjects who had a primary current diagnosis of SCH, MDD, or BP1 as defined by DSM-5 criteria were included. Only subjects who were cooperative, already on a stable dose of aripiprazole and likely to be capable of using DMS technology were included into the trial. In addition, the patients were rated as mildly ill on the CGI-S (mean 3.1, SD 1) and exhibited only mild functional difficulties (mean on the PSP scale 76.6; SD 12.9). Furthermore, the recruited population had a mean of 13.7 years of education.

Treatments

In this study, the version of DMS (now referred to as Abilify MyCite system) evaluated was the IEM and DW5 patch combination (/DW5) with the DMS software application Version 1.5.3.

Objectives

The primary objective of the study was the functionality of the integrated call center. The primary endpoint was defined as the frequency of inbound and outbound calls.

Outcomes/endpoints

Primary Endpoint

The primary outcome variable was the establishment of a functional and operational integrated call centre with coordinated feedback to the subject and investigative site to optimize the use of DMS as measured by:

- Inbound calls (i.e., calls from the subject to the integrated call centre) by help type;
- Outbound calls (i.e., calls from the integrated call centre to the subject) by help type.

Sample size

The sample size determination is not based on statistical but rather on practical considerations. It should be noted that the unit of observation fundamental to the primary objective is the call center. Consequently, the sample size of the study could be considered 1.

Randomisation and blinding (masking)

The study was an open-label, uncontrolled study. Therefore, no randomisation was performed. In addition, no blinding procedures were applicable.

Statistical methods

Datasets for Analysis
The following analysis samples are defined for this trial:
- Enrolled sample: All subjects who sign an ICF and enter the trial.
- Safety sample: All subjects who enter the trial and use the Digital Medicine System.
- Intent-to-treat (ITT) sample: All subjects who enter the trial and use the Digital Medicine System.
- Observation Phase sample: All subjects who enter the 6-week observation phase.

For the primary variable, the analysis was conducted based on the ITT sample.

Analysis methods - specified in the statistical analysis plan - are limited to descriptive statistics of call frequency, separated by several stratification factors (help/call type, disease type, study time and gender).
Analysis of exploratory endpoints is limited to descriptive statistics as well. Consequently, external validity of results is limited.

Results

In total, 49 subjects were enrolled to the study and 38 subjects completed the study.

The most frequent reason for discontinuation was noncompliance with patch wearing (n= 4). In addition, another patch-associated reason (non-adherence of the patch to the skin) led to the discontinuation of two subjects. All subjects were included in efficacy and safety analyses. Other reasons for discontinuation were lost to follow up (n= 1), subject decision to withdraw (n= 2), physician decision (n= 1) and non-adherence of the patch to the skin (n=2).

Recruitment

Date of first signed informed consent/ Trial initiation date: 08 Mar 2016; Date of last trial observation/ Trial completion date: 08 Sep 2016

Conduct of the study

According to the applicant the trial was conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. No protocol amendments and deviations occurred in this trial.

Baseline data

- **Demographic characteristics**

Patients with BP1, MDD and SCH were recruited into the study. The mean age of the population was 46.4 years. They had a mean of 13.7 years of education and all of the patients were fluent in English. The mean disease duration was 9.2 years and all of the patients were on a stable dose of aripiprazole. The baseline CGI-S score was 3.1

Psychiatric History and Baseline Psychiatric Scale Evaluations

Subjects had BP1 (22 subjects), MDD (12 subjects), or schizophrenia (15 subjects), and they had their disease for a mean of 9.2 years. The mean baseline CGI-S score was 3.1 (1.0) and the mean baseline PSP total score was 76.6 (12.9).

- **Baseline Medications**

Overall, 95.9% (47/49) of enrolled subjects reported using one or more medications prior to the start of trial treatment. Overall, the most frequently reported class of prior medication was pyschoanaleptics (e.g., trazodone, citalopram hydrobromide, venlafaxine hydrochloride), taken by 51.0% (25/49) of subjects.

Numbers analysed

The ITT population consisted of 49 subjects. All subjects were analysed for efficacy and safety.

Outcomes and estimation

Primary endpoint

The primary objective of the study was the functionality of the integrated call centre. The primary endpoint was defined as the frequency of inbound and outbound calls.

In total, the subjects made 136 inbound calls and received 257 outbound calls. Most of the inbound calls were due to pill status tile (37.5%) and issues with the patch (12.5%). Most of the outbound calls were due to issues with the patch (55.3%), followed by other issues (14%, including the two routine outbound calls per subjects) and pill related issues (10.5%).

79.6% of the subjects received outbound calls because of issues with the patch, showing that nearly all of the subjects faced patch related issues during the study. Apart from the routine calls, most of the outbound calls were triggered due to technical issues with the patch (47.1%).

Ancillary analyses

N/A

Summary of main efficacy results

The following table summarises the efficacy results from study 316-14-220 supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4: Summary of efficacy for trial 316-14-220

Title: 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			
Study identifier	316-14-220 (The study was published by Peters-Stickland et al. 2016.)		
Design	This was an open-label trial to evaluate the usability of the MIND1 System by adult subjects with schizophrenia.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 weeks not applicable not applicable
Hypothesis	Exploratory: to measure the usability of the MIND1 System by adult subjects with schizophrenia (SCH) with regards to the ability to replace and pair the Patch independently and successfully.		
Treatments groups	Open-label		The drug-device combination consisted of a tablet of aripiprazole (10, 15, 20, or 30 mg) plus the embedded IEM. All subjects took aripiprazole + IEM tablets during the treatment period of this trial. 8 weeks in duration, with 67 subjects enrolled.
Endpoints and definitions	Primary endpoint	Pair and apply patch independentl y	The proportion of subjects who were able to pair and apply a patch independently and successfully by the end of the Week 8 trial visit (or early termination if applicable), as defined as a score of 91 to 100 on the Subject Ability to Use System Scale - Healthcare Professional Version (SAUSS-HCP).
	Secondary endpoint	Apply patch with minimal assistance	Proportion of subjects who were able to pair and apply a patch successfully by the end of the Week 8 trial visit (or early termination if applicable) independently or with minimum assistance, as defined by a SAUSS-HCP score of 71 to 100.
	Secondary endpoint	Duration to wear patch regularly	Proportion of time during the trial period when subjects wore their patches; the time duration of patch wearing was calculated based on digital health data.

	Other endpoints	Other endpoints	• The time to the first occurrence of the subject being able to pair and apply the patch independently and successfully; • The support level the subject needed from a caregiver/support person, as applicable, as assessed using a Caregiver/Support Person Involvement Scale;* • Levels of satisfaction as measured by a Subject Satisfaction Scale; • Perceived usability as measured by a Healthcare Professional Usability Assessment Scale and a Subject Usability Scale, as well as a Caregiver/Support Person Involvement Scale (as applicable*); • The proportion of days subjects used the application and the proportion of days investigators and/or other trial site staff used the healthcare professional portal during the trial;** • The frequency of Call Center support by help type; • The proportion of ingested IEMs registered on digital health data server versus expected IEMs ingested; • CGI-S change from baseline; • CGI-I over time; • PGI-I over time; • PANSS total score change from baseline; • • The safety and tolerability of the MIND1 System, as assessed by the frequency and severity of AEs, device-related AEs, SAEs, AEs leading to discontinuation, and unanticipated adverse device effects. *This endpoint was not assessed due to the low number of caregivers/support persons in Cohort 1 and the absence of caregivers/support persons in Cohort 2. **This endpoint was not assessed because the relevant technology to generate usage duration data was not yet available.
Database lock	07 Jul 2015		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Intent to treat and Safety (are the same in this study). The study includes a screening period (≤ 2 weeks), a treatment period (8 weeks), and a safety follow-up period (2 weeks); thus, the total duration of an individual subject's participation in this study is up to 12 weeks.	
Descriptive statistics and estimate variability	Treatment group	ITT Group (Total)
	Number of subject	67
	Pair and apply patch independently (%)	37 (55.2%) were able to pair and apply a patch independently and successfully by Week 8 (95% CI, 42.6%, 67.4%) as defined as a score of 91 to 100 on the SAUSS-HCP. Results varied across sites (from 26.7% to 73.3%), but were similar between Cohorts 1 and 2

	Apply patch with minimal assistance (%)		55 (82.1%) subjects were able to pair and apply a patch independently or with minimal assistance by Week 8 (95% CI, 70.8%, 90.4%) as defined by a SAUSS HCP score of 71 to 100. Results were similar across Cohorts 1 and 2
	Duration to wear patch regularly [mean (SD)]		70.7% (24.7%) of the trial period and a median of 77.8% of the trial period
	Other endpoints		• For all questions on the Subject Satisfaction scale, the majority of subjects chose a favorable response (at Week 8 and at last visit). For example, at Week 8, ~66% of subjects responded that use of the MIND1 System was somewhat easy, easy, or extremely easy; ~70% indicated that it was somewhat helpful, helpful, or extremely helpful in management of their condition; and ~79% felt it was somewhat helpful, helpful, or extremely helpful in improving discussions with their doctor (and others in the treatment team). At Week 8, ~81% of subjects were somewhat satisfied, satisfied, or extremely satisfied with the system and ~68% would be somewhat likely, likely, or extremely likely to use it in the future (if available and recommended by their doctor). • Total Call Center help at Week 1 was required by 60.0% subjects and was lower for subsequent weeks (down to 39.2% of subjects at Weeks 6/7). • Most treatment-emergent AEs (TEAEs) reported during the trial were mild.
Effect estimate per comparison **Not applicable as this is an open-label exploratory study**	<Co->Primary endpoint	Comparison groups	<group descriptors>
		<test statistic>	<point estimate>
		<variability statistic>	<variability>
		P-value	<P-value>

Table 5: Summary of efficacy for trial 316-13-215

Title: A Multicenter, 8-week, Open-label, Single-arm, Exploratory Trial to Assess the Functionality of an Integrated Call Center for the Digital Medicine System by Adult Subjects With Schizophrenia (SCH), Major Depressive Disorder (MDD), or Bipolar 1 Disorder (BP1) Who Are Treated With Oral Aripiprazole			
Study identifier	316-13-215 (The study was published by Peters-Stickland et al. 2016.)		
Design	This was an open-label trial to evaluate the usability of the MIND1 System by adult subjects with schizophrenia (SCH).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 weeks not applicable not applicable
Hypothesis	Exploratory: to assess the functionality of an integrated call center for optimizing use of the MIND1 system by adult subjects with SCH.		
Treatments groups	Open-label		The drug-device combination consisted of a tablet of aripiprazole (10, 15, 20, or 30 mg) plus the embedded IEM. All subjects took aripiprazole + IEM tablets during the treatment period of this trial. 8 weeks in duration, with 49 subjects enrolled.
Endpoints and definitions	Primary endpoint	Inbound calls	To assess the functionality of an integrated call center for the Digital Medicine System (DMS) by adult subjects with SCH, major depressive disorder (MDD), or bipolar 1 (BP1) who were treated with oral aripiprazole.
Database lock	08 Sep 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) and Safety (are the same in this study) Screening period (≤ 7 days), an assessment period (8 weeks), and a safety follow-up period (1 week)		
Descriptive statistics and estimate variability	Treatment group		ITT Group (Total)
	Number of subjects		49

	Inbound calls N (%)		36 (73.5%) of subjects made inbound calls to the center, most frequently for reasons related to pill status tile (40.8%, 20/49), account creation (22.4%, 11/49), issues with the patch (18.4%, 9/49), and status icon or patch status (18.4%, 9/49). Some subjects made more than 1 call, the most frequent overall reasons for inbound calls were pill status tile (37.5%, 51/136 calls), issues with the patch (12.5%, 17/136 calls), and status icon or patch status (8.8%, 12/136 calls).
	Outbound calls N (%)		49 (100%) of subjects received an outbound call
	Patch coverage time mean (SD)		77.91 (17.55)
	Days with good patch coverage [Mean (SD)]		80.14 (19.66)
	IEM Ingestion [Mean (SD)]		71.00 (20.07)
Effect estimate per comparison **Not applicable as this is an open-label exploratory study**	<Co->Primary endpoint	Comparison groups	<group descriptors>
		<test statistic>	<point estimate>
		<variability statistic>	<variability>
		P-value	<P-value>
	<<Co->Primary ><Secondary><other: specify> endpoint	Comparison groups	<group descriptors>
		<test statistic>	<point estimate>
		<variability statistic>	<variability>
		P-value	<P-value>
	<<Co->Primary ><Secondary><other: specify> endpoint	Comparison groups	<group descriptors>
		<test statistic>	<point estimate>
		<variability statistic>	<variability>
		P-value	<P-value>
Notes	There were no statistical analysis issues to report for this study.		
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**		
	Not applicable		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable. In studies 316-14-220 and 316-13-215 only subjects aged 18 to 65 years were included.

Supportive studies

According to the applicant, the Abilify MyCite clinical development programme consisted of 6 clinical exploratory trials, and 9 human factors (HF) studies.

The 6 exploratory trials are:

- **Trial 316-13-204**: A Formative Usability Study of the Otsuka MIND1 Prototype by Subjects With Bipolar Disorder or Major Depressive Disorder.
- **Trial 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.
- **Trial 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.
- **Trial 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.
- **Trial 316-13-215**: A Multicenter, 8-week, Open-label, Single-Arm, Exploratory Trial to Assess the Functionality of an Integrated Call Center for the Digital Medicine System by Adult Subjects With Schizophrenia (SCH), Major Depressive Disorder (MDD), or Bipolar 1 Disorder (BP1) who are Treated With Oral Aripiprazole.
- **Trial 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.

Whereas the CSRs of the two clinical studies 316-13-215 and 316-14-220 have been submitted and at least a short description of the 4 other clinical studies has been provided in the dossier, no information at all was available in the original submission concerning the 9 HF studies (not even the study titles were cited). As also these studies were part of the clinical development program of Abilify MyCite, for the sake of completeness, the applicant was requested to also provide a short description of these 9 HFs including a discussion of the obtained results and their impact on the development of the current Abilify MyCite system.

The applicant followed the request and submitted a tabulated summary of these 9 HF studies (see Table 4.2.1-1 D150 Clinical AR). According to the applicant, these studies were designed to assess and reduce use risks, while improving effectiveness of the system. In addition, the results of these studies were used to support the development of the version to be marketed in the EU.

The applicant´s response is acknowledged. However, no HF or usability study was carried out investigating the safe use of the Abilify MyCite system intended to be marketed in the proposed patient population. In addition, apparently more supportive clinical or HF studies have been conducted in the clinical development program of Abilify MyCite than described by the applicant in the dossier. The applicant should provide information on all clinical or HF studies, which have been part of the clinical development program of Abilify MyCite. The studies should be shortly summarised and the full study reports should provided.

3.3.5. Discussion on clinical efficacy

The evidence base to support the present MAA and thus, the claimed indication for Abilify MyCite consists of two therapeutic exploratory trials, studies 316-14-220 and 316-13-215, conducted in the US exclusively.

Both studies utilized different versions of the Abilify MyCite system. The differences between these versions and the current to be marketed one have not been addressed anywhere in the original dossier. In addition, it was unknown which actual Abilify MyCite system (IEM, Patch including proprietary IEM and Patch software, App/Cloud Software, size of the sensor, size of the patch, adhesive component, etc.) was intended for authorisation in the EU as no description of it was provided anywhere in the original submission. Upon request of the Rapporteurs, the applicant provided for the first time in this application procedure information concerning the drug-device system intended to be commercialized in the EU. Hence, it turned out that a completely different version of the Abilify MyCite system compared to the ones utilized in any of the submitted studies is intended to be authorized. The proposed product will not only use different software applications (EU v2.0.0; different MyCite App with new reminder function), but also utilizes a completely different patch, the 2-piece reusable patch (adhesive strip with embedded battery and reusable data pod containing the electronics; only the adhesive strip is disposed after one week). By contrast, in the pivotal and all other previous clinical studies either the RP4 or DW5 one-piece disposable patches were used (data pod is integrated in the adhesive strip, the whole patch is disposed after one week). As a result, the instructions for use differ remarkably for the patch as compared with the other two disposable patches (e.g. the reusable data pod has to be placed securely in the adhesive strip before use of the patch and removed from the adhesive strip after one week at the latest, when the strip needs to be changed). With this regard, it needs to be pointed out, that neither the usability (or functionality) of the Abilify MyCite system to be commercialised nor even only the pairing and applying of its patch has been investigated by the applicant in any of the clinical studies conducted so far. In addition, for the patch the composition of the adhesive material was changed. The conclusion of the applicant that the patch thus provokes less skin irritations is not supported by any clinical data. See D150 Clinical AR for the detailed information on all differences.

Design and conduct of clinical studies

Study 316-14-220

In this uncontrolled, open-label trial, the usability of two different previous versions of the Abilify MyCite system to be marketed (then called MIND1 system) was investigated in two different cohorts of patients with schizophrenia. From the D120 responses provided by the applicant, it can be concluded that the MIND1 system differs significantly with regard to its usability from the to be marketed Abilify MyCite system, in particular concerning the use of the patch (see above).

All patients were trained for 3 weeks before they were left alone to use the system correctly, and during a subject's participation in the trial, a Call Centre and trial site staff were available for

assistance, if needed. Thus, it was questioned if these study settings reflect the real-world use of the drug-device combination as for example, neither the presence of Call Center was described in the PI nor for how long patients need to be trained to use the system correctly. The applicant was asked if a standardized training or assistance during use is foreseen and if not, how it can be ensured that patients use the system appropriately. However, from the applicant´s response it remains unclear, how long the targeted population needs to be trained to set-up and use the drug-device system correctly. No standardized training seems to be planned, patients are intended to be instructed by their physicians and/or staff (it also remains questionable, if the HCP receive any training). Patients are further encouraged to use the MyCite App, in which training material is included, and a call centre is planned to be established.

Altogether, the applicant's response strengthens the concern that the use of the Abilify MyCite system is complex and that training and assistance is needed for proper use.

The study protocol had a major protocol amendment once (introduction of another version of the MIND1 system during study conduct) when the trial was already well under way. Amongst other things, also the primary endpoint was modified. Several protocol deviations occurred, in particular dosing errors and procedural deviations affecting primary outcome variables. Overall, all of these protocol changes - in particular those concerning the treatment administered and the primary endpoint - during trial conduct are seen rather critical to impact the evaluation of study data and the reliability of the results.

Substantial differences were noted between the original Statistical Analysis Plan (dated October 1 2014, prior to the database lock of Cohort 1 on 24 Dec 2014) and the final version of the Statistical Analysis Plan (dated July 21, 2015 - about 2 weeks after the last observation from Cohort 2), which need to be clarified.

In study 316-14-220, only patients with schizophrenia, who were on a stable aripiprazole dose before trial initiation, were cooperative, motivated and willing to use the system were included. In addition, these patients had a relatively low level of impairment. All patients were also capable of using a smartphone. Therefore, the results of this study may not be generalizable to a more typical population of patients with schizophrenia (i.e. more severe or acutely ill patients, patients with high levels of delusional symptoms or suspiciousness, patients with low illness insight. In addition, the participants were recruited from sites in the US only; usability in a non-English speaking population was not tested.

The **primary objective** of this trial was solely the evaluation of the ability of adult subjects with schizophrenia to successfully and independently apply a wearable sensor (patch) on their torso and pair the patch with the relating smartphone application (App) by the end of 8 weeks of treatment (including a 3-week training phase). Thus, the study only evaluated the **usability of the patch** with regard to its correct application and pairing with the MyCite App.
The **primary endpoint** of the present study which was defined as the proportion of subjects who were able to pair and apply a patch independently and successfully by the end of the Week 8 trial visit (or early termination if applicable), as defined as a score of 91 to 100 on the SAUSS-HCP.
The **key secondary endpoint** was defined as the proportion of subjects who were able to pair and apply a patch successfully by the end of the Week 8 trial visit (or early termination if applicable) independently or with minimum assistance, as defined by a SAUSS-HCP score of 71 to 100.

Study objectives and endpoints do not substantiate the claim "to measure medication adherence". In addition, the patient population for evaluation the usability of the MIND 1 system is not considered representative for the broader population proposed in the PI.

Only 55.2% (37/67) of patients included in the present trial were able to pair and apply the patch independently and successfully by the end of Week 8 trial visit, receiving a score of 91 to 100 on the

SAUSS-HCP 100-point scale. Another 26.9%, corresponding to 18 individuals were successful with minimal assistance. This suggests that many subjects with schizophrenia, even in a cohort that is relatively mildly ill, have difficulties to handle the drug-device system. In addition, it has to be taken into account that these patients received 3-weeks of training to use the system.

Nevertheless, what might be derived from these data despite all limitations, is that the correct use of the drug-device-system, even of only the patch, seems to be rather difficult for patients without receiving any training. It noticeable, however, that also after one week of training the results improved only slightly in Cohort 2 (3 out of 29 patients were able to use the patch correctly then). It is unclear how the training of the patients was performed and if it was done under standardized conditions.

According to the results provided, 55 out of 67 patients (82.1%) achieved the secondary endpoint, i.e. were able to pair and apply a patch successfully by the end of the Week 8 trial visit independently or with minimum assistance.

However, the assessment of the primary and key secondary endpoint is strongly criticised, limiting or even making the overall interpretation of its results impossible.

The SAUSS-HCP score, on which the primary and one secondary endpoint are based, is not validated and does not meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness (cf. ICH E8 General Considerations for Clinical Trials):

- The individual categories of this scale seem highly subjective and no standards seem to have been defined for each category.
- It is unclear if there could have been overlaps as no detailed explanation was provided for the descriptors of the categories: for example, it is unclear what is meant with "minimal assistance" / "moderate help" / "significant assistance" needed. It is also unknown how overlaps have been handled for the presentation of results.
- In addition, several categories with different scores are named in the same way: e.g. "moderate, reasonable understanding", "minimal good understanding".
- It remains completely unclear, how the score points were awarded to the patients: e.g. if a patient was able to place and pair the patch independently and successfully by Week 8, did he/she score 100 points? Or 92, 93… points? What was the decision of assigning e.g. 100 instead of 91 points to a patient based on, was it fulfilment of all criteria of the primary endpoint? The same applies for all other categories.
- In addition, it is entirely unclear what the difference between the primary and secondary endpoint is with respect to the following wording: "independently and successfully" and "independently or minimal assistance". Hence, if a patient was able to pair and apply a patch independently without any assistance wasn´t he/she also successful in doing so or why was he only rated as "independently" but not as "successfully"? What was the difference for example, between "minimal and moderate assistance"? It is very likely that overlaps occurred between categories, but their handling is unclear.
- Primary and secondary endpoints were based on a dichotomization of the score. For the primary endpoint the cut-off was set at 90 – meaning responders were able to independently place/pair; for the secondary endpoint it was set at 70 – meaning responders were permitted to receive minimal assistance. In this regard, clinical relevance of "minimal assistance" is unclear. Subjects who only require minimal assistance may nevertheless be unable to use the system on their own. This needs to be taken into account in the interpretation of response - especially concerning results in the secondary endpoint.

Finally, success was determined by the best score observed during the trial, i.e., at any single post-baseline visit. This means that a subject that failed at the last visit of the study was still scored as "success", if he had been successful on a previous occasion. There is a risk that this approach overestimates the usability of the system.

It is further unclear to what extent the underlying concept of usability is relevant to technical and clinical performance of the system. Specifically it is unclear to what degree certain usability levels would ensure sufficient quality of reception for the patch to detect IEM ingestion, as well as quality of connection for the phone to offload registered data. As stated with regard to objectives, clinical implications of adherence monitoring are entirely disregarded by the assessment.

Concerning measurement of patch wear time, the definition used appears objective and assuming technical reliability in terms of step tracking could serve as a lower bound. Nevertheless, issues with study population (subjects with mild conditions, required to be generally compliant) and study procedures (patches were paired/placed in the presence of study personnel) seriously hamper the external validity of related estimates. I.e. it is entirely unclear whether patch wear times recorded in an idealized study setting, with a highly selected study population could be representative for real world use cases.

The above described deficiencies severely affect the validity and reliability of the presented results and hamper the clinical interpretation of the primary and secondary endpoints. Importantly, their relevance to the claimed indication and ability to reflect potential patient benefit is questioned.

It is further noticeable, that the results varied across the 6 trial sites considerably (from 26.7% to 73.3%). A centre effect could be a possible reason. However, interpretation of these results is hampered due to the very low patient number in each trial site (for example, in site 6 only 4 patients were enrolled in total for both cohorts) which precludes drawing any reliable conclusions.

The exploratory endpoint "ability to wear the patch regularly" revealed that subjects of both cohorts wore the patch for a mean of 70.7% (24.7%) of the trial period. The average wearing time per patch per subject in days was 3.6 (SD 1.6). This is considered rather short since according to instructions given in the SmPC, the patch is intended for use of up to one week. It also implies that subjects might have faced some problems with wearing the patch (e.g., it maybe have fallen off or subjects experienced adverse events because of the patch, like a rash etc., or maybe the patch was uncomfortable etc.). When looking at the data of both cohorts separately, mean patch wearing time was even shorter for Cohort 2 versus Cohort 1 (66.2% vs 74.4%, respectively). Consequently, also more patches per subject were used in Cohort 2 (10.3; SD 4.8) compared to Cohort 1 (9.1; SD 4.0). As a different version of the MIND1 system was used in Cohort 2, including another patch probably composed differently (e.g. different glue in its adhesive stripe etc.) this might have been one reason for the observed differences between the two cohorts.

Several other usability scale were used in the study, to assess the other exploratory endpoints. These scales however, have all the same limitations as the SAUSS-HCP scale. Altogether, what might be derived from their results is, that is seems rather difficult, even for patients with mild cognitive impairments, to correctly use the patch, despite the fact that subjects received a 3 weeks training and had assistance available throughout the trial.

The above described deficiencies and the additionally observed major amendments and protocol deviations (i.e. amendment 1 concerning introduction of the second MIND 1 system during the study, change in the description/assessment of the primary and key secondary endpoint applying and using the SAUSS-HCP score, etc.) severely question the reliability of the data and hamper the overall interpretation of the obtained results. The only conclusion is that most likely assistance is needed when using the drug-device-combination - even in not severely ill patients. However, as the trial does not

support the claimed indication "to measure medication adherence", the identified deficiencies will not be further pursued.

It was further noticeable, that, in total, also only 93.2% of the IEMs of the placebo + IEM tablets were registered. The applicant clarified that patients even under supervision might not have taken a tablet+IEM. As this, might have been the case several times, the study conduct seems rather questionable and further hampers the overall interpretation of the obtained results.

In conclusion, it is severely doubted that this system can be effectively and safely used to measure medication adherence in clinical practice (as claimed by the applicant). Overall, it appears that the drug-device system has a high risk of obtaining false negative results, which might lead to potential intake of extra doses and overdosing. Taking extra doses / overdoses was now identified by the applicant as potential hazard of Abilify MyCite, supporting the major concerns raised by the Rapporteurs with this respect.

The PI does not specify the intended duration of treatment and the applicant responded that they do not intend to make a clear statement on it, which is not acceptable .

Study 316-13-215

Trial 316-13-215 was an open-label, single-arm trial, conducted in adult subjects with SCH, BP1, or MDD. The primary objective of the study was to assess the functionality of an integrated call centre for the digital medicine system. The exploratory objectives of the trial were patch wear time, ingested IEMs, CGI-score, subject and HCP engagement, and subject satisfaction with the system. Although the design of the study is adequate to show the functionality of an integrated call centre that might be helpful in setting up the DMS and providing support with further questions, the study objectives do not allow to draw any conclusions on patient adherence and thus, to support the claimed indication.

Subjects with a primary current diagnosis of SCH, MDD, or BP1 as defined by DSM-5 criteria were eligible for the study, but only if they were cooperative, already on a stable dose of aripiprazole and likely to be capable of using DMS technology. The baseline CGI-S score of the recruited population was rather low; apparently, only mildly ill patients were recruited. The assessment phase consisted of a two-week prospective phase and a 6-week observational phase. Only subjects who adhered to the system in the prospective phase (i.e. with ≥50% patch wear time in the last 7 days before Week 2 visit) were allowed to continue into the observation phase. Thus, there was a pre-selection of "good performers", both at study enrolment and during the prospective phase of the study. This would need to be reflected in the SmPC, since the broad target population, for which an indication is currently sought, was not sufficiently represented in the clinical trial.

The primary objective of the study was the functionality of the integrated call centre. The primary endpoint was the frequency of inbound and outbound calls. The clinical relevance of the measurement of inbound and outbound calls as a variable for assessment of the primary outcome needs to be further explained. Most of the inbound calls were due to pill status tile (37.5%) and issues with the patch (12.5%). The high portion of calls due to pill status tile implies that there could have been discrepancies between pill intake and status displayed on the smartphone, which may have led to confusion on pill intake. In a worst-case scenario, this could lead to overdosing.

On the other hand, most of the outbound calls were due to issues with the patch (55.3%) and affected 79.6% of the subjects. As nearly all subjects faced patch-related issues during the study it seems that there may be a fundamental problem with the patch. Additionally, the exploratory endpoint "patch coverage and adherence" revealed that the subjects wore the patch for a mean of 77.91% of the time.

This implies that subjects faced some problems with wearing the patch. The high number of subjects that had technical problems with the patch requires further discussion.

It is also questioned how the call centre would be integrated in the "real-life treatment" of patients. It seems likely that without the call centre, the patch wearing times would be even worse. The applicant is asked to elaborate on the function of the call-centre in a real-life setting.

With regard to endpoints describing subjects, sample size does have implications on the precision of estimates. To this end, the number of subjects was not justified based on statistical considerations on sensitivity or precision. The number of subjects enrolled into the trial is considered rather low.

Regarding the claimed indication of measuring medication adherence, the applicant states that subjects had a mean of 71% of days with ingested IEMs registered on the digital health data server and that this percentage would even be higher (88.57%) if only assessing days with good patch coverage. However, days with bad patch coverage (subjects did not wear the patch at about 20% of the time) cannot simply be ignored.

This is further strengthened by the discrepant results from the analysis of treatment compliance (defined as [amount of trial medication used]/ [amount of expected trial medication]*100%). While results based on CRF data indicate that 91.8% of the subjects have more than 90% compliance, digital health data show that only 16.3% of the subjects have more than 90% compliance. This discrepancy indicates that based on the digital health data, no reliable conclusion on treatment compliance can be drawn. Besides patients not wearing the patch, this might have reasons such as connectivity issues with the smartphone, poor patch adherence or subjects not pairing the patch with the app properly. In addition, the individual patient data listings reveal that the first ingestion of the IEM was not detected in 12 of 49 patients, indicating that the set-up and the implementation of the system poses problems.

The choice of the primary and exploratory endpoints might be adequate for establishment of the integrated call centre providing help and feedback to the subject to set up the DMS. However, the selection and definition of the primary and all other endpoints in the context of the study design do not allow drawing conclusions on patient adherence and thus, cannot support the claimed indication.

3.3.6. Conclusions on clinical efficacy

The applied indication for Abilify MyCite differs from the approved indication for Abilify® tablets without sensor with respect to demography (adolescents not included) and the additional claim to measure medication adherence.

However, the studies 316-14-220 and 316-13-215 neither address/support the label claim nor were they conducted in a patient population representative of the broad target population. There was no baseline assessment of non-adherence or efficacy evaluation in terms of improvement of adherence. Deficiencies and shortcomings with regard to trial design and conduct of both studies severely affect the overall interpretation of their results. In none of the studies, the Abilify MyCite system intended to marketed was used, which differs remarkably from the previous versions with regard to its usability and functionality.

Overall, results do not allow drawing reliable conclusions on any impact on patient adherence to aripiprazole medication with the Abilify MyCite system in its present form/function. The applicant´s response further strengthens the concern, that the use of the Abilfy MyCite system seems to be very complicated and that training and assistance is needed during use. With this regard several concerns remain to be resolved.

3.3.7. Clinical safety

The clinical trial program for the Proteus Digital Health Feedback System was initiated by Proteus Digital Health in Jan 2008, and aimed to characterize the safety and technical performance of the device. As per the Proteus Instructions for Use a total of 492 subjects have participated in clinical trials representing 6407 days of Personal Monitor use with or without sensor ingestion. Six clinical trials have been conducted with the components of the Abilify MyCite system (Table 6).

However, the safety data is primarily based on two Studies that used the *complete Abilify MyCite medicinal product and device Combination*:

- Trial 316-13-215 (Aripiprazole Plus Sensor and Personal Monitor in Subjects with Schizophrenia, Bipolar 1 Disorder, or MDD)
- Trial 316-14-220 (Aripiprazole Plus Sensor and Personal Monitor in Subjects with Schizophrenia)

The safety assessment in these clinical trials focussed on adverse events collection, vital signs monitoring, physical examination, concomitant medication and suicidality.

According to the Investigator's Brochure of ingestible sensor (FDA-cleared device label, LBL-0171 Instruction for Use Proteus Digital Health Feedback Device DW5), a total of 492 subjects have participated in clinical trials representing 6407 days of Personal Monitor use with or without sensor ingestion.

Table 6: Safety Evaluations in Abilify MyCite Trials

Protocol	Adverse Event Reporting	Clinical[a] Laboratory Tests	Vital Signs	Physical Examination	ECG
316-13-204	Screening, baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16, follow-up (Week 20)	Screening only (pregnancy test)	Screening, baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16	Baseline only	--
316-13-205	Screening, baseline, Days 8, 15, 22, 29	Screening, baseline, Day 29 (chemistry, hematology, urinalysis); pregnancy test[b] every visit	Screening, baseline, Day 29	Screening, baseline, Day 29	Screening only
316-13-206a	Screening, Day 1, follow-up (Day 15)	Screening only (chemistry, hematology, urinalysis); and pregnancy test[b]	Screening , Day 1	Screening only	--
316-13-206b	Screening, Day 1, follow-up (Day 7)	Screening, Day 1 (pregnancy test[b] only)	Screening , Day 1	Screening only	--
316-13-215	Screening, baseline, Weeks 2, 4, 8, follow-up (Week 9)	Screening (pregnancy test[b] only)	Screening, baseline, Weeks 2, 4, 8	Screening only	--
316-14-220	Screening, baseline, Weeks 1, 2, 3, 4, 8, follow-up (Week 10)	Screening only (chemistry, hematology, urinalysis); pregnancy test[b]	Screening, baseline, Weeks 1, 2, 3, 8	Screening only	Screening only

[a]In addition, urine drug screening was performed at screening (Trials 316-13-204, 316-13-206a, 316-13-206b, 316-14-220) or at screening and baseline (Trial 316-13-205).

[b]Pregnancy tests for Trial 316-13-205 at screening, baseline, Days 8, 15, 22, 29, 57; for Trials 316-13-206a and 316-13-206b, at screening and also on Day 1 (if screening occurred > 72 hours before Day1); for Trial 316-13-215 at screening; for Trial 316-14-220 at screening, baseline, Weeks 1, 2, 3, 8.

-- = Not performed, as per the protocol.

Source: CSR 316-13-204, Section 16.1.1; CSR 316-13-205, Section 16.1.1; CSR 316-13-206a, Section 16.1.1; CSR 316-13-206b, Section 4.1.1; CSR 316-13-215, Section 16.1.1; CSR 316-14-220, Section 16.1.1.

Patient exposure

In trial 316-14-220, 65 subjects received at least on dose of IMP and in trial 316-13-215, 49 subjects received at least one dose of IMP (Table 7 and Table 8). In both trials, all subjects receiving at least on dose of the IMP were included in the safety database. The mean duration of exposure was 47.3 days in trial 316-14-220 and 47 days in trial 316-13-215. While trial 316-13-215 enrolled patients with BP1, MDD and SCH and therefore representing the population for which the indication is sought for, trial 316-14-220 only included SCH patients.

Table 7: Extent of exposure Trial 316-14-220

	Cohort 1 N=37	Cohort 2 N=30	Total N=67
No. of subjects with ≥ 1 dose of aripiprazole + IEM	35	30	65
Total Duration of Exposure			
Mean (SD)	47.4 (14.1)	47.1 (15.0)	47.3 (14.4)
Median	55.0	55.0	55.0
Min, max	7, 57	7, 62	7, 62

Table 8: Extent of exposure Trial 316-13-215

	BP1 N=22	MDD N=12	SCH N=15	Total N=49
No. of subjects with ≥ 1 dose of aripiprazole + IEM	22	12	15	49
No. of days of exposure				
Mean (SD)	46.9 (18.5)	48.3 (19.4)	46.1 (17.3)	47.0 (18.0)
Median	56.0	55.5	54.0	55.0
Min, max	9, 60	1, 64	12, 60	1, 64

Note: eCRF data were used as the source for this summary table.

Only Trials 316-13-215 and 316-14-220 used the complete Abilify MyCite medicinal product and device combination. The 4 additional exploratory studies were product development trials intended to develop the communication flow from the Personal Monitor to the app and aripiprazole was only administered in Study 316-13-206a. Trials 316-13-205, 316-13-206a, and 316-13-206b were conducted in healthy subjects, whereas Trial 316-13-204 was performed in patients with bipolar disorder or MDD.

Adverse events

Trial 316-14-220

Adverse events are summarized in Table 9. Overall, 37 of 67 (55.2%) subjects experienced TEAEs during the trial and 22 of 67 (32.8%) subjects experienced device-associated TEAEs. Overall, 2 subjects experienced serious TEAEs, 1 subject experienced a severe TEAE, and 6 subjects discontinued from the trial due to an AE. No subjects died during the trial and there were no pregnancies during the trial or AEs related to suicidal ideation or suicide.

Table 9: Summary of Adverse events Trial 316-14-220

Parameter	Cohort 1 N=37 n (%)	Cohort 2 N=30 n (%)	Total N=67 n (%)
Subjects with AEs	22 (59.5)	15 (50.0)	37 (55.2)
Number of AEs	36	28	64
Subjects with TEAEs	22 (59.5)	15 (50.0)	37 (55.2)
Subjects with device-associated TEAEs	13 (35.1)	9 (30.0)	22 (32.8)
Subjects with medication-associated TEAEs	12 (32.4)	9 (30.0)	21 (31.3)
Number of TEAEs	34	28	62
Subjects with serious TEAEs	2 (5.4)	0 (0.0)	2 (3.0)
Subjects with severe TEAEs	1 (2.7)	0 (0.0)	1 (1.5)
Subjects discontinued from the trial due to AE	2 (5.4)	4 (13.3)	6 (9.0)

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 eCRF. Device-associated AEs were those reported on the adverse device event page of the eCRF. Device-associated AEs could have been associated to any part of the MIND1 System (except aripiprazole).

Treatment-emergent Adverse Events

The incidence of device-associated TEAEs is summarized in Table 10. Device-associated TEAEs were those events reported on the adverse device events page of the CRF. Overall, 22 of 67 (32.8%) subjects experienced device-associated TEAEs; furthermore, all 22 of these subjects had device-associated TEAEs that were considered by the investigator to be related to the device. The most frequently occurring device-associated TEAE was pruritus (9 of 67 subjects, 13.4%). One subject had a device-associated TEAE that was considered severe; this TEAE of rash, which lead to discontinuation from the trial.

Table 10: Incidence of device-associated, treatment-emergent adverse events Trial 316-14-220

System Organ Class MedDRA Preferred Term	Cohort 1 N=37 n (%)	Cohort 2 N=30 n (%)	Total N=67 n (%)
Any device-associated TEAE	**13 (35.1)**	**9 (30.0)**	**22 (32.8)**
Gastrointestinal disorders			
Diarrhoea	0 (0.0)	1 (3.3)	1 (1.5)
Nausea	0 (0.0)	1 (3.3)	1 (1.5)
Infections and infestations			
Abscess	1 (2.7)	0 (0.0)	1 (1.5)
Injury, poisoning, and procedural complications			
Excoriation	1 (2.7)	0 (0.0)	1 (1.5)
Nervous system disorders			
Paraesthesia	1 (2.7)	0 (0.0)	1 (1.5)
Skin and subcutaneous tissue disorders			
Pruritus	5 (13.5)	4 (13.3)	9 (13.4)
Erythema	2 (5.4)	2 (6.7)	4 (6.0)
Rash	3 (8.1)	0 (0.0)	3 (4.5)
Dermatitis contact	2 (5.4)	1 (3.3)	3 (4.5)
Rash erythematous	2 (5.4)	0 (0.0)	2 (3.0)
Blister	1 (2.7)	0 (0.0)	1 (1.5)
Rash papular	0 (0.0)	1 (3.3)	1 (1.5)
Rash pruritic	0 (0.0)	1 (3.3)	1 (1.5)
Skin discolouration	0 (0.0)	1 (3.3)	1 (1.5)
Skin hyperpigmentation	0 (0.0)	1 (3.3)	1 (1.5)
Skin irritation	0 (0.0)	1 (3.3)	1 (1.5)

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 eCRF. Device-associated AEs could have been associated to any part of the MIND1 System (except aripiprazole).

Medication-associated TEAEs were those events reported on the AE page of the CRF. Overall, 21 of 67 (31.3%) subjects experienced medication-associated TEAEs (Table 11). The most frequently occurring medication-associated TEAEs were upper respiratory tract infection and hypertension, which were experienced by three subjects each (4.5%). No subject had a medication-associated TEAE that was considered severe.

Table 11: Incidence of medication-associated, treatment-emergent adverse events Trial 316-14-220

System Organ Class MedDRA Preferred Term	Cohort 1 N=37 n (%)	Cohort 2 N=30 n (%)	Total N=67 n (%)
Any medication-associated TEAE	**12 (32.4)**	**9 (30.0)**	**21 (31.3)**
Cardiac disorders			
Tachycardia	0 (0.0)	1 (3.3)	1 (1.5)
Gastrointestinal disorders			
Constipation	1 (2.7)	0 (0.0)	1 (1.5)
Diarrhoea	1 (2.7)	0 (0.0)	1 (1.5)
Dry mouth	1 (2.7)	0 (0.0)	1 (1.5)
Toothache	0 (0.0)	1 (3.3)	1 (1.5)
General disorders and administration-site conditions			
Malaise	0 (0.0)	1 (3.3)	1 (1.5)
Infections and infestations			
Upper respiratory tract infection	3 (8.1)	0 (0.0)	3 (4.5)
Nasopharyngitis	1 (2.7)	0 (0.0)	1 (1.5)
Kidney infection	0 (0.0)	1 (3.3)	1 (1.5)
Investigations			
Blood pressure increased	1 (2.7)	1 (3.3)	2 (3.0)
Blood pressure systolic increased	1 (2.7)	0 (0.0)	1 (1.5)
Metabolism and nutrition disorders			
Increased appetite	0 (0.0)	2 (6.7)	2 (3.0)
Nervous system disorders			
Somnolence	0 (0.0)	2 (6.7)	2 (3.0)
Transient ischaemic attack	1 (2.7)	0 (0.0)	1 (1.5)
Akathisia	0 (0.0)	1 (3.3)	1 (1.5)
Drooling	0 (0.0)	1 (3.3)	1 (1.5)
Extrapyramidal disorder	0 (0.0)	1 (3.3)	1 (1.5)
Psychiatric disorders			
Agitation	1 (2.7)	0 (0.0)	1 (1.5)
Respiratory, thoracic, and mediastinal disorders			
Sinus congestion	1 (2.7)	0 (0.0)	1 (1.5)
Vascular disorders			
Hypertension	3 (8.1)	0 (0.0)	3 (4.5)

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.

- **Treatment-emergent Adverse Events Related to the Drug-device**

Overall, 22 of 67 (32.8%) subjects experienced a patch-related TEAE. The most frequently occurring patch-related TEAE was pruritus (9 of 67 subjects, 13.4%), followed by erythema (4 of 67 subjects, 6.0%). One subject had a patch-related TEAE that was considered severe (rash, which lead to discontinuation from the trial).

Other Significant Events

- **Concomitant Medications**

Overall, 55 of 67 (82.1%) enrolled subjects reported using one or more medications during the treatment period. The most frequently reported classes of concomitant medication (i.e., those used by >15% of subjects overall) were: psycholeptics taken by 32.8% of subjects, psychoanaleptics taken by 35.8% of subjects, and agents acting on the renin-angiotensin system taken by 17.9% of subjects.

- **Assessment of Suicidality**

Assessment of suicidality by the Columbia-Suicide Severity Rating Scale revealed that no subjects had completed suicide or showed suicidal behavior during study 316-14-220. Three subjects reported suicidal ideation during the course of the study. No TEAEs occurred that were related to suicidal ideation or suicide.

Trial 316-13-215

In trial 316-13-215, 21 subjects (42.9%) had at least one AE during the study and 20 subjects (40.8%) had at least one TEAE. 34.7% of the subjects experienced device-associated TEAEs and 16.3% of the subjects experienced medication-associated TEAEs. All of the device-associated TEAEs were found to be patch-related TEAEs. Adverse events are summarized in Table 12. One subject discontinued from treatment due to an AE (mild, nonserious erythema). No subjects died during the trial and no subjects had a serious or severe TEAE (Table 12). There were no pregnancies or AEs related to suicidal ideation or suicide during the trial.

Table 12: Summary of Adverse events Trial 316-13-215

Parameter	BP1 N=22 n (%)	MDD N=12 n (%)	SCH N=15 n (%)	Total N=49 n (%)
Number of AEs	15	14	3	32
Number of TEAEs	12	14	2	28
Subjects with				
AEs	11 (50.0)	9 (75.0)	1 (6.7)	21 (42.9)
TEAEs	10 (45.5)	9 (75.0)	1 (6.7)	20 (40.8)
Device-associated TEAEs	9 (40.9)	8 (66.7)	0 (0.0)	17 (34.7)
Medication-associated TEAEs	2 (9.1)	5 (41.7)	1 (6.7)	8 (16.3)
Serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation from DMS due to AE	1 (4.5)	0 (0.0)	0 (0.0)	1 (2.0)

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 events reported on the AE page of the eCRF as "general" AEs. Device-associated AEs were events reported on the AE page of the eCRF as "device" AEs. Device-associated AEs could have been associated to any part of DMS (except aripiprazole).

- **Treatment-emergent Adverse Events**

The incidence of device-associated TEAEs is summarized in Table 13. Device-associated TEAEs were events noted on the AE page of the eCRF to be "device" AEs. Overall, 17 of 49 (34.7%) subjects experienced device-associated TEAEs; furthermore, all 17 of these subjects had device-associated TEAEs that were considered by the investigator to be related to the device. The most frequently occurring device-associated TEAE was rash (22.4%, 11/49 subjects). The majority of the device-associated TEAEs were mild in severity, and none was severe.

Table 13: Incidence of device-associated, treatment-emergent adverse events Trial 316-13-215

System Organ Class MedDRA Preferred Term	BP1 N=22 n (%)	MDD N=12 n (%)	SCH N=15 n (%)	Total N=49 n (%)
Any device-associated TEAE	**9 (40.9)**	**8 (66.7)**	**0 (0.0)**	**17 (34.7)**
Nervous system disorders				
Hyperaesthesia	1 (4.5)	0 (0.0)	0 (0.0)	1 (2.0)
Skin and subcutaneous tissue disorders				
Rash	5 (22.7)	6 (50.0)	0 (0.0)	11 (22.4)
Erythema	2 (9.1)	0 (0.0)	0 (0.0)	2 (4.1)
Pruritus	1 (4.5)	1 (8.3)	0 (0.0)	2 (4.1)
Skin irritation	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.0)

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 events reported on the AE page of the eCRF as "device" AEs. Device-associated AEs could have been associated to any part of DMS (except aripiprazole).

The incidence of medication-associated TEAEs is summarized in Table 14. Medication-associated TEAEs were those events noted on the AE page of the eCRF to be "general" AEs (i.e., not device-associated AEs). Overall, 8 of 49 (16.3%) subjects experienced medication-associated TEAEs; none of the medication-associated TEAEs experienced by these subjects were considered related to the drug-device. None of the medication-associated TEAEs were severe in intensity.

Table 14: Incidence of medication-associated, treatment-emergent adverse events Trial 316-13-215

System Organ Class MedDRA Preferred Term	BP1 N=22 n (%)	MDD N=12 n (%)	SCH N=15 n (%)	Total N=49 n (%)
Any medication-associated TEAE	2 (9.1)	5 (41.7)	1 (6.7)	8 (16.3)
Gastrointestinal disorders				
Nausea	1 (4.5)	0 (0.0)	0 (0.0)	1 (2.0)
General disorders and administration site conditions				
Peripheral swelling	0 (0.0)	0 (0.0)	1 (6.7)	1 (2.0)
Infections and infestations				
Sinusitis	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.0)
Upper respiratory tract infection	1 (4.5)	1 (8.3)	0 (0.0)	2 (4.1)
Injury, poisoning and procedural complications				
Meniscus injury	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.0)
Sunburn	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.0)
Musculoskeletal and connective tissue disorders				
Pain in extremity	0 (0.0)	0 (0.0)	1 (6.7)	1 (2.0)
Nervous system disorders				
Headache	1 (4.5)	1 (8.3)	0 (0.0)	2 (4.1)
Syncope	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.0)

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 events reported on the AE page of the eCRF as "general" AEs (ie, they were not device-associated AEs).

- **Treatment-emergent Adverse Events Related to the Drug-device**

Overall, 17 of 49 (34.7%) subjects experienced a device-associated TEAE that was related to the drug-device). Similarly, 17 of 49 (34.7%) subjects experienced a patch-related TEAE, which were the same preferred terms as the device-associated TEAEs. No device-associated TEAEs were related to the IEM or to the phone app.

Other Significant Events

- **Concomitant Medications**

Overall, 47/49 enrolled subjects (95.9%) reported using one or more medications during the trial. The most frequently reported classes of concomitant medication overall were: psychoanaleptics taken by 51.0% (25/49) of subjects, anti-epileptics taken by 30.6% (15/49) of subjects, psycholeptics taken by 30.6% (15/49) of subjects, and lipid-modifying agents taken by 22.4% (11/49) of subjects.

- **Assessment of Suicidality**

Assessment of suicidality by the Columbia-Suicide Severity Rating Scale revealed that no subjects had completed suicide or showed suicidal behavior during study 316-13-215. Two subjects reported suicidal ideation during the study. No TEAEs occurred that were related to suicidal ideation or suicide.

Serious adverse events and deaths

No deaths occurred during any of the 6 exploratory trials described in the SCS.

According to the applicant, 6 subjects experienced serious TEAEs, which occurred during Trials 316-13-204 and 316-14-220; none of the serious TEAEs were related to the IMP/test product. During Trial 316-13-204, 4 of 58 (6.9%) subjects experienced a serious TEAE. For the event of major depression, use of the device was interrupted; no action was taken for the other events. During Trial 316-14-220, 2 of 67 (3.0%) subjects experienced a serious TEAE. For the event of agitation, the drug/device was withdrawn; no action was taken with the test product for the event of transient ischaemic attack. No subject experienced a serious TEAE during the other 4 trials.

Table 15: Subjects with Serious Treatment-emergent Adverse Events

Subject Number (Age/Gender/Race)	Serious TEAE Outcome Term(Onset)Causality/	Trial	Day	SeverityTest Preferred Action Taken	Product
Trial 316-13-204					
	Tooth abscess		Moderate	Not related/ None	Recovered/ resolved
	Periorbital cellulitis		Moderate	Not related/ None	Recovered/ resolved
	Bacteraemia		Severe	Not related/ None	Recovered/ resolved
	Hallucination		Moderate	Not related/ None	Recovered/ resolved
	Major depression		Severe	Not related/ Device interrupted	Recovered/ resolved
Trial 316-14-220					
	Transient ischaemic attack		Moderate	Not related/ None	Recovered/ resolved
	Agitation		Moderate	Not related/ Drug-device withdrawn	Recovered/ resolved

M = male; F = female.

Laboratory findings

Clinical laboratory tests were performed in the 6 trials at the time points shown in Table 16. As noted below, laboratory tests were planned and performed for postbaseline time points only for Trial 316-13-205.

No pregnancies were reported in the 6 trials described in the SCS.

Table 16: Clinical Laboratory Test Evaluations in Abilify MyCite Trials

316-13-204	316-13-205	316-13-206a	316-13-206b	316-13-215	316-14-220
Screening only (pregnancy test)	Screening, baseline, Day 29 (chemistry, hematology, urinalysis); pregnancy test[b] every visit	Screening only (chemistry, hematology, urinalysis); and pregnancy test[b]	Screening, Day 1 (pregnancy[b] test only)	Screening (pregnancy test[b] only)	Screening only (chemistry, hematology, urinalysis); pregnancy test[b]

a In addition, urine drug screening was performed at screening (Trials 316-13-204, 316-13-206a, 316-13-206b, 316-14-220) or at screening and baseline (Trial 316-13-205).
b Pregnancy tests for Trial 316-13-205 at screening, baseline, Days 8, 15, 22, 29, 57; for Trials 316-13-206a and 316-13-206b, at screening and also on Day 1 (if screening occurred > 72 hours before Day1); for Trial 316-13-215 at screening; for Trial 316-14-220 at screening, baseline, Weeks 1, 2, 3, and 8.

Vital signs

Vital signs were assessed in the 6 trials at the time points shown in Table 17.

Table 17: Vital Signs Evaluations in Abilify MyCite Trials

316-13-204	316-13-205	316-13-206a	316-13-206b	316-13-215	316-14-220
Screening, baseline, Weeks 2, 4, 6, 8, 10, 12, 14, 16	Screening, baseline, Day 29	Screening, Day 1	Screening, Day 1	Screening, baseline, Weeks 2, 4, 8	Screening, baseline, Weeks 1, 2, 3, 8

Overall, the following vital signs TEAEs occurred (which, with the exception of the abnormality described above, did not meet the criteria for potential clinical relevance): 2 of 67 (3.0%) subjects with blood pressure increased; 1 of 67 (1.5%) subjects with blood pressure systolic increased; and 3 of 67 (4.5%) subjects with hypertension.

Physical examinations

Physical examinations were performed in the 6 trials at the time points shown in Table 18. There were no physical examination findings of clinical concern in any of the trials.

Table 18: Physical Examinations in Abilify MyCite Trials

316-13-204	316-13-205	316-13-206a	316-13-206b	316-13-215	316-14-220
Baseline only	Screening, baseline, Day 29	Screening only	Screening only	Screening only	Screening only

Electrocardiograms

Electrocardiograms were performed only for Trials 316-13-205 and 316-14-220 (at screening), as noted in Table 19.

Table 19: Electrocardiogram Evaluations in Abilify MyCite Trials

316-13-204	316-13-205	316-13-206a	316-13-206b	316-13-215	316-14-220
--	Screening only	--	--	--	Screening only

-- = Not performed, as per the protocol.

Electrical Safety

The FDA recognizes International Electrotechnical Commission (IEC) 60601-1, namely Medical Electrical Equipment – Part 1: General Requirements for Safety, as its cornerstone for addressing key hazards associated with electrical medical equipment. IEC 60601-1 aims to protect both patients and users by reducing the likelihood of such hazards. Proteus Digital Health, Inc. therefore uses this standard as its primary guideline to design and test its devices from an electrical safety perspective. Where appropriate, IEC 60601-1 has been applied to components of the Proteus Device, in order to ensure conformance with critical safety requirements

Furthermore, theoretical analysis and empiric in-vivo testing confirmed that the IS is not capable of causing near- or far-field tissue stimulation, due to the very small amount of, and nature of, the current created by ISs. In-vivo testing also demonstrated that the IS does not cause electrochemical damage to the lumen of the gastrointestinal tract.

Mechanical Safety

No mechanical injury has been observed preclinically or reported in human studies. In clinical studies up to 4 ISs have been ingested simultaneously without harm.

According to the Investigational Brochure for ingestible sensor, the size of a single IS at the time of ingestion is similar to a single grain of sand. Mechanical safety tests were performed in a canine model, which indicated that ISs: 1) cause no mechanical injury to the lumen of the gastrointestinal tract and 2) are excreted reliably. A total of 120 ISs (delivered within gelatin capsules) have been administered (40 ISs/day for 3 days) orally to an animal model, and no mechanically-related injuries to the GI tract were observed upon pathological analysis. IS device excretion has been assessed in an animal model; ingested ISs were reliably excreted, with a total gut transit time comparable to that reported in literature.

The following is an excerpt from the FDA-cleared device label (LBL-0171 Instruction for Use Proteus Digital Health Feedback Device DW5) which summarizes the technical performance:

A total of 412 study subjects have participated in Pill ingestion studies representing 20,993 ingestible sensor ingestions. In comparison with direct observation, the ingestible sensor was detected in 97.3% of ingestions, with correct identification in 100%.

The latest configuration of the Ingestible Event Marker (IEM) IC version DP5.1 incorporated into the Miniature IEM in Tablet (MIT) dose form—underwent formative testing in PROMITTER 47. 'Adjusted' Positive Detection Accuracy (PDA, analogous to sensitivity) was 99.7% (367 detected/368 ingested under direct observation, 95%CI 98.5% - 100.0%). The 'adjusted' number removes detections and

missed detections that occurred when the cleared compatible medical device was known to be functioning improperly, while the 'all-inclusive' number includes these events. In this study, 24 ingestions across 3 subjects were excluded in the adjusted PDA analysis, due to unstable impedance measurements (which can indicate poor apposition of the cleared compatible medical device to the skin). The 'all-inclusive' PDA (no data points excluded) was 99.0% (388 detected/392 ingested under direct observation, 95%CI 97.4% - 99.6%). There were no false positives.

Safety in special populations

No information on special populations has been given. Abilify MyCite has not been studied in children or adolescents and not adults ≥65 years of age in Studies 215 and 220. The intended use is for adults only. One of the inclusion criteria was "Male and female subjects 18 to 65 years of age."

Immunological events

No information has been given on the immunogenicity of Abilify MyCite. This is acceptable, as no immunological reaction is to be expected.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been submitted with the dossier. The drug-drug interactions listed in the SmPC are in line with the reference medicinal product.

Discontinuation due to AES

No subject experienced a TEAE leading to discontinuation from the trial during Trials 316-13-205, 316-13-206a, and 316-13-206b.

The incidence of TEAEs leading to discontinuations in the remaining 3 trials was:

- Trial 316-13-204, 2 of 58 (3.4%) subjects
- Trial 316-13-215, 1 of 49 (2.0%) subjects
- Trial 316-14-220, 6 of 67 (9.0%) subjects

Table 20: 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
Trial 316-13-204					
	Applicationsite rash		N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
	Applicationsite erythema		N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
Trial 316-13-215					
	Erythema		N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
Trial 316-14-220					
	Agitation		Y/ Moderate	Not related/ Drug-device withdrawn	Recovered/ resolved
	Rash		N/ Severe	Related/ Drug-device withdrawn	Recovered/ resolved
	Rash papular		N/ Moderate	Related/ Drug-device withdrawn	Recovered/ resolved
	Pruritus		N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
	Skin discolouration		N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
	Rash pruritic		N/ Mild	Related/ Drug-device withdrawn	Recovered/ resolved
	Drooling		N/ Moderate	Related/ Drug-device withdrawn	Recovered/ resolved

One subject experienced a TEAE resulting in discontinuation of the drug-device (Subject) who experienced a mild, nonserious TEAE of erythema (verbatim term, redness at patch site) on Day 9, which was related to the drug-device. This event was rated Grade 2 on an 8-point (Grades 0-7) skin irritation scale; higher numbers on this scale indicated more skin irritation. The subject had no other AEs.

In Study 220, 6 subjects experienced a total of 7 TEAEs resulting in discontinuation of the drug/device (2 subjects in Cohort 1, 4 subjects in Cohort 2). Of these events, one event (agitation) was serious. Most of the TEAEs resulting in discontinuation of the drug/device (i.e., 5 of 7 events) were device-associated and all were in the skin and subcutaneous tissue disorders SOC (rash, rash papular, pruritus, skin discolouration, and rash pruritic; Table 20).

No data on the DAEs in Study 204 was provided by the applicant.

Listings of discontinued subjects for any reason, i.e. including DAEs, in studies 215 and 220 have been copied into the Clinical AR from subject data listings of the CSRs.

Post marketing experience

Abilify MyCite has recently been approved by the FDA. Four Periodic Adverse Drug Experience Reports (PADERs) have been submitted, but no new information was provided within these PADERs.

3.3.8. Discussion on clinical safety

The safety data is primarily based on two studies that used the Abilify MyCite drug and device combination (Aripiprazole plus Sensor and Personal Monitor): Trial 316-13-215 (in subjects with Schizophrenia, Bipolar 1 Disorder and MDD) and Trial 316-14-220 (in subjects with Schizophrenia). The primary objectives of the study were the usability of the device and the functionality of an integrated call centre. While trial 316-13-215 enrolled patients with BP1, MDD and SCH, trial 316-14-220 only included SCH patients. Additionally, information on the level of summary tables for the 4 additional exploratory studies on healthy volunteers or patients with BP1, MDD, or schizophrenia was submitted by the applicant. The exploratory studies were small, almost all were non-controlled and had an open-label single arm design.

The safety assessment in both clinical trials focussed on adverse events collection, vital signs monitoring, physical examination, concomitant medication and suicidality. In trial 316-14-220, 65 subjects received at least on dose of IMP and in trial 316-13-215, 49 subjects received at least one dose of IMP. In both trials, all subjects receiving at least on dose of the IMP were included in the safety database. The extent of exposure is rather low in both trials. The mean duration of exposure was 47.3 days in trial 316-14-220 and 47 days in trial 316-13-215. Due to the short duration of both trials (8 weeks), no conclusion on possible long-term safety implications with the used system can be drawn. Furthermore, treatment duration is not specified in the proposed SmPC.

In trial 316-14-220, 37 subjects (55.2%) had at least one AE during the study and 37 subjects (55.2%) had at least one TEAE. 32.8% of the subjects experienced device-associated TEAEs and 31.3% of the subjects experienced medication-associated TEAEs. All of the device-associated TEAEs were found to be patch-related TEAEs. Of the 22 subjects who experienced device-associated TEAEs, nine subjects suffered from pruritus, four from erythema, three from rash, three from contact dermatitis and two from erythematous rash. While most of the patch-related TEAEs were considered mild or moderate, one subject experienced severe rash, which led to the discontinuation from the trial. In total, six subjects had to discontinue from MIND 1 due to TEAES, the reasons for discontinuation being rash, papular rash, pruritus/skin discolouration, pruritic rash, agitation and drooling. One of the TEAEs that led to discontinuation from the trial was considered severe (rash).

No deaths were reported in the trial. Two subjects (3%) experienced serious treatment-emergent adverse events, with one suffering from transient ischaemic attack and the other suffering from agitation. Both serious TEAEs were not related to study drug. While no action was taken with the test product for the event of transient ischaemic stroke, the drug/device was withdrawn for the event of agitation.

In trial 316-13-215, 21 subjects (42.9%) had at least one AE during the study and 20 subjects (40.8%) had at least one TEAE. 34.7% of the subjects experienced device-associated TEAEs and 16.3% of the subjects experienced medication-associated TEAEs. All of the device-associated TEAEs were found to be patch-related TEAEs. Of the 17 subjects who experienced device-associated TEAEs, 11 subjects suffered from rash, two from erythema, two from pruritus and one from skin irritation. These TEAEs were further rated on an 8-point skin irritation scale, with 8 subjects having Grade 1 skin irritation (minimal erythema, barely perceptible), 7 subjects having Grade 2 skin irritation (definite erythema, readily visible; minimal edema or minimal papular response), and 1 subject having Grade 3 skin irritation (erythema and papules).

One subject had to discontinue from DMS due to an AE (erythema). The erythema was patch-related. The subject had been re-applying the patch to the same spot, instead of placing a new patch in a different spot each week. It was questioned if the space where the patch can be applied is too limited and therefore there might be a high probability for developing skin irritations. In the D120 responses, the applicant argued that they expect an improved subject experience with the to-be marketed patch version, as it could be worn on different areas of the abdomen. However, as no data were generated with this new version of the patch this assumption remains hypothetical.

The analyses of AEs in the two clinical trials indicate that many subjects experience treatment related AEs associated with the patch. The use of the patch might provoke skin and subcutaneous tissue disorders that might even lead to treatment discontinuation. Compared with using Aripiprazole alone, the use of the Aripiprazole plus Sensor and Personal Monitor system comes with an increased risk of device-associated TEAEs related to the patch use. In addition, the patch intended for marketing has not been tested with regard to skin tolerance.

In both trials, most of the enrolled subjects reported use of one or more concomitant medication (82.1% of subjects in trial 316-14-220 and 95.9% in trial 316-13-215). The most frequent co-medications were psychoanaleptics, psycholeptics, anti-epileptics, lipid-modifying drugs and agents acting on the renin-angiotensin system. It is not clear whether the use of co-medications might have any implications for the functionality of the digital medicine system. Specifically, the applicant should address the question if certain drugs for acid related disorders (like calcium carbonate, omeprazole or ranitidine) that might change the gastric acid milieu, could affect the functionality of the drug device system which activation seems to depend on gastric pH.

Assessment of suicidality was done using the Columbia-Suicide Severity Rating Scale. No subject committed suicide or showed suicidal behaviour during the studies; 2 subjects reported suicidal ideation during study 316-13-215 and 3 subjects reported suicidal ideation during study 316-14-220. Again, the short duration of the studies does not allow drawing any conclusion on long-term safety.

The data on clinical laboratory tests, vital signs, physical examination, electrocardiogram and Physical examinations is sparse and were mainly performed at screening. It is not possible to assess these safety aspects based on the limited data.

Additionally, the following safety concerns need to be taken into account:

- No clinical safety data are available for the drug-device system intended to be marketed. This system differs remarkably from the Abilify MyCite versions investigated in both pivotal studies (see also D150 Clinical AR for a detailed description of the differences).
- The influence of food on the detection of the signal remains unknown. The respective statement in the proposed SmPC that Abilify MyCite can be taken with or without food can still not be verified based on the data provided by the applicant.
- Overdosing: In study 316-13-215, the individual patient data listings reveal that the first ingestion of the IEM was not detected in 12 of 49 patients. In study 316-14-220 the protocol deviation listings show that 6 of 67 subjects took an overdose. Therefore, it seemed as if overdosing is a potential risk when applying the Abilify MyCite medicinal product. Upon request, the applicant outlined that multiple extrinsic (e.g. poor skin contact of the patch, poor Bluetooth connectivity etc.) and intrinsic factors (user errors) may contribute to a missed or delayed detection of the IEM signal by the smartphone app. Therefore, the applicant himself now identified overdose as an important potential risk.
- Excretion: The applicant does not provide any clinical data on the excretion of the IEM. Although it is stated in the clinical overview that safety tests in a canine model indicated that the IEM was

excreted reliably and did not cause mechanical injury to the lumen of the gastrointestinal tract, it is not entirely clear on which data this statement is based on and what the term "excreted reliably" means in this regard. In the submitted clinical studies, patients were not monitored for the excretion of the IEM. In humans, the development of diverticuli (patients suffering from diverticulitis) might be a potential depot for the IEMs. This could lead to inflammation and perforation of the diverticulum, ultimately requiring surgery. This remains an uncertainty in the use of the product.

- Detection in obese patient: Upon request of the Rapporteurs, the applicant did not provide any information about the range of the signal (in cm) from the sensor. The mean BMI in study 316-14-220 was 31.9 kg/m2 and the mean BMI in study 316-13-215 was 35.9 kg/m2. It remains questioned whether the detection of the signal might be compromised in obese subjects.

3.3.9. Conclusions on clinical safety

In addition to the adverse events of Aripiprazole already described in the original marketing authorization, the Abilify MyCite system causes skin and subcutaneous tissue disorders related to the use of the patch. In addition, there are no clinical safety data available with the to-be marketed Abilify MyCite system.

Furthermore, there seems to be a potential risk of overdosing when applying the Abilify MyCite system. The applicant outlined that multiple extrinsic (e.g. poor skin contact of the patch, poor Bluetooth connectivity etc.) and intrinsic factors (user errors) may contribute to a missed or delayed detection of the IEM signal by the smartphone app and included overdose as an important potential risk.

Thus, the safety profile of Abilify MyCite and particularly the long-term safety of its use is currently not satisfactorily justified. The applicant has to address and resolve the issues detailed in the LoOI. Additionally, some adaptations of the SmPC are considered necessary.

3.4. Risk management plan

Post-authorisation data should be presented in detail in *Module SV – Post-authorisation Experience* of the RMP.

3.4.1. Safety Specification

Summary of safety concerns

Table 21: Summary of safety concerns

Summary of safety concerns	
Important identified risks	EPS, including tardive dyskinesia
Important potential risks	Orthostatic hypotension Overdose in certain situations of device malfunction (device) Device Malfunction (including ingestible sensor, personal monitor, and smartphone application) (device)
Missing information	Use in pregnancy and lactation Use in elderly patients (≥65 years of age)

Discussion on safety specification

Assessor's comment:

As part of the EU Renewal procedure for Abilify Maintena, the safety concerns of this product were re-assessed and re-classified. The RMP was updated as a result and submitted to EMA as RMP version 11.1. The EMA Committee for Medicinal Products for Human Use (CHMP) provided a positive opinion for the reclassification of the risks. European Commission (EC) approval was granted on August 27, 2018.

The proposed safety concerns are appropriate, even if for the important identified risk "EPS, including tardive dyskinesia" and for the important potential risk "Orthostatic hypotension" no further evaluation in the pharmacovigilance plan and no additionally risk minimisation measures are planned.

The safety and efficacy of Abilify MyCite in the treatment of schizophrenia or manic episodes in bipolar I disorder in patients aged 65 years and older has not been established and there are no adequate and well-controlled trials of aripiprazole in pregnant women. Therefore, it is endorsed that "Use in elderly patients (≥65 years of age)" and "Use in pregnancy and lactation" are included in the list of safety concerns as missing information.

Missed or delayed detection of ingestible sensor signal by the smart phone application can potentially tempt the patient to take an additional dose. Therefore, overdose is included in the list of safety concerns as important potential risk.

The potential occurrence of technical issues and the failure of the interaction between the ingestible sensor and the human-machine interface (smartphone) and the consequent impact on the patient ("device") is included as important potential risk in the RMP (Device Malfunction (including ingestible sensor, personal monitor, and smartphone application).

Conclusions on the safety specification

The two safety concerns related with the device could be merged to "Overdose due to device malfunction (including ingestible sensor, personal monitor, and smartphone application) (device)".

3.4.2. Pharmacovigilance Plan

Routine pharmacovigilance activities

There are no routine PV activities beyond adverse reactions reporting and signal detection for Abilify MyCite.

Summary of planned additional PhV activities from RMP

There are no ongoing or planned additional pharmacovigilance activities for Abilify MyCite.

Regarding the missing information of Use in Elderly Patients above 65 Years of Age, patients 65 years old and above have not been sufficiently included in human factor or clinical studies of Abilify MyCite (less than 9 patients in 138 patients with 50 years old or above, and much more between 18 and 50). Therefore, the applicant should propose an additional pharmacovigilance activity to further monitor / characterise the safety profile of this medicinal product in this population considering that the usage of Abilify MyCite is different and more complex than the usage of Abilify tablets.

Overall conclusions on the PhV Plan

The applicant should propose a post-authorisation PhV development plan to characterize the safety in in patients above 65 years old.

3.4.3. Risk minimisation measures

Routine Risk Minimisation Measures

Information regarding the identified safety concerns is communicated in the product label for the approved indications. Reports of AEs from patients receiving Abilify MyCite are closely monitored to identify and characterize AEs and to identify any emerging safety issues. Risk minimisation measures are planned for each important identified or potential risk as described in table below.

Summary of additional risk minimisation measures

The routine risk minimisation activities as described in the table below are considered by the applicant to be sufficient to manage the safety concerns of Abilify MyCite.

Table 22: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Extrapyramidal symptoms (EPS), including tardive dyskinesia	Routine risk minimisation measures: - Special warnings and precautions for use, section 4.4 of SmPC - Undesirable effects, section 4.8 of the SmPC	Routine
Orthostatic Hypotension	Routine risk minimisation measures: - Undesirable effects, section 4.8 of the SmPC	Routine
Overdose in certain situations of device malfunction	Routine risk minimisation measures: - Special warnings and precautions for use, section 4.4 of SmPC (detection of ingestion) - Undesirable effects, section 4.8 of the SmPC - Overdose, section 4.9 of the SmPC - Instructions for using the Abilify MyCite system, Package Leaflet Other routine risk minimisation measures beyond the product information: - Provision of instructions for use for HCP, patients and caregivers	Routine

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	- Smartphone application Instruction for use (video) - Smartphone application medication notification **Abilify MyCite system support:** - Technical Support (call centre)	
Device Malfunction (including ingestible sensor, personal monitor, and smartphone application)	Routine risk minimisation measures: - Special warnings and precautions for use, section 4.4 of SmPC (detection of ingestion) - Instructions for using the Abilify MyCite system, Package Leaflet Other routine risk minimisation measures beyond the product information: - Provision of instructions for use for HCP, patients and caregivers - Smartphone application Instruction for use (video) - Smartphone application medication notification **Abilify MyCite system support:** - Technical Support (call centre)	Routine
Use in Pregnancy and Lactation	Routine risk minimisation measures: - Pregnancy and lactation, section 4.6 of the SmPC	Routine
Use in Elderly Patients above 65 Years of Age	Routine risk minimisation measures: - Posology and method of administration, section 4.2 of the SmPC - Special warnings and precautions for use, section 4.4 of SmPC - Instructions for using the Abilify MyCite system, Package Leaflet	Routine

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Other routine risk minimisation measures beyond the product information: - Provision of instructions for use for HCP, patients and caregivers - Smartphone application Instruction for use (video) - Smartphone application medication notification **Abilify MyCite system support:** - Technical Support (call centre)	

The applicant does not consider provision of additional information to HCP and patients, besides SmPC, PL and the instructional video associated to the smartphone application. There are several caveats to this proposal, as described below.

1- When the HCP proposes the use of such a distinctive and innovative procedure, there should be a leaflet to support this. The SmPC targets HCPs and is inadequate for the caregiver or patient, and PL is only accessible at the time of purchasing or acquisition, and thus not adequate for the initial discussion.

2- The PL aim is to describe how to use and the consequences of use that lay people should be aware of, and not to discuss the inherent philosophy behind its use. This is critical in psychiatric population in need of an antipsychotic. These patients frequently have paranoid delusions regarding medication and poisoning, and an explaining leaflet may ease their concerns.

3- The instructional video in the smartphone App may change at applicants will, and the patient may not access it due to several reasons. Even if the video is mandatory when installing the application, it is not possible to know that the patient / caregiver were attentive. Therefore, presenting / education material should be prepared and be available upon marketing.

As such, an education material is required as detailed above.

It is noted that this additional risk minimisation measure should be linked in the RMP to the applicable safety concerns (e.g. Overdose in certain situations of device malfunction (device) and to Device Malfunction (including ingestible sensor, personal monitor, and smartphone application) (device)).

Regarding the routine risk minimisation measure of the Smartphone application medication notification, which is described in the RMP as:

> *The smartphone Medication Notification is available to patients on the smartphone application two hours after the scheduled time of the missed medication ingestion. This feature is intended to remind the patient to take their medication in case the patient missed a dose of a medication. Additionally, the Medication Notification allows the patient to respond to the Notification by answering "I took the medication", which gives the patient an opportunity to*

communicate with their HCP and to confirm that the tablet was taken in the event of missed or delayed detection of the ingestible sensor due to a technical failure. The patient's response to the Notification will be communicated to the HCP through the Abilify MyCite web-based Portal.

Patients are provided with training on the use of the smartphone Medication Notification and informed that it allows them to communicate with the clinician about any unexpected missed medication ingestions. Subsequently, patients will receive training to help them recognize that the ingestible sensor can take time to register. As this Medication Notification appears in the smartphone application within 2 hours after the patient's original scheduled dose time, patients would be more likely to remember whether they actually took the medication.

The applicant should clarify what training is to be provided to the patient and how is this training performed.

On the other hand, there is also no reference to any technical support (call center) in the Instructions for using the Abilify MyCite system, provided in the PL so it is not clear how will the patients access further support if needed. This should be resolved.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are not sufficient to minimise the risks of the product and supplementary risk minimisation measures are required:

- An educational material is required to explain the rationale for Abilify MyCite and to present Abilify MyCite to future users (patients / caregivers), in order to address the potential risks related to overdose and device malfunction.

On the other hand, there is also no reference to any technical support (call center) in the Instructions for using the Abilify MyCite system, provided in the PL so it is not clear how will the patients access further support if needed. This should be resolved.

3.4.4. Summary of the risk management plan

The public summary of the RMP may require revision.

PRAC Outcome

The PRAC generally supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report and agreed that the RMP for Ability MyCite (aripiprazole) in the proposed indication could be acceptable provided that an update to RMP version 1.1 and satisfactory responses to the questions detailed in the List of outstanding issues - D180 are provided.

The PRAC discussed the challenges for some groups of patients, including those too poor to afford a smartphone or those with low digital literacy, to handle the device. It is emphasized that this product will only be used for a selected group of patients who are able to use the application and those who have a low risk of trust issues with carers and health professionals. Clear instructions for population selection should be included in the PI.

In terms of additional pharmacovigilance, the PRAC considered that the safety profile of aripiprazole is well characterised and that no further studies are needed.

As for risk minimisation measures, the PRAC agreed with the proposals from the rapporteur. The MAH should ensure that the smart phone app instructions are different from the "instructions for use". While the first will provide guidance on how to use the app, the later should focus on the risk of overdose and should be available for the initial discussion prescriber-patient. Both should be categorised as additional risk minimisation measures.

It is also agreed that the "call centre" and the "Smartphone App medication notification" should not be classified as risk minimisation measures.

The PRAC also noted that two safety concerns related with the device could be merged to "Overdose due to device malfunction (including ingestible sensor, personal monitor, and smartphone application) (device)". Although overdose may not reflect all the impacts of device malfunction, such as for instance, underdose or delayed administration, it is accepted that overdose is the main risk.

3.4.5. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 7.4.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4. Significance/Non-Conformity of paediatric studies

Not applicable.

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The applicant applied for the following indication:

"Abilify MyCite is a drug-device combination product comprised of aripiprazole tablet embedded with an ingestible sensor ***to measure medication adherence****.*

Abilify MyCite is indicated in adults for the treatment:

- *for the treatment of schizophrenia,*

- *for the treatment of moderate to severe manic episodes in bipolar I disorder, and*
- *for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment."*

The proposed indication for Abilify MyCite is similar to the approved indication for Abilify®, except that the proposed indications is for adults only with the additional claim to measure medication adherence.

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. Schizophrenia typically begins in late adolescence or early adulthood. It can impair functioning through the loss of capability to earn a livelihood or disruption of studies.

Bipolar I Disorder is defined by manic episodes that last at least seven days (most of the day, nearly every day) or when manic symptoms are so severe that hospital care is needed. Usually, separate depressive episodes occur as well, typically lasting at least two weeks. Episodes of mood disturbance with mixed features (having depression and manic symptoms at the same time) are also possible.

Schizophrenia and BP1 are chronic mental illnesses, with excessive physical comorbidity and greatly reduced life expectancy compared with the general population (De Hert et al. 2011). The active phases of the disorders are associated with highly debilitating symptoms; severe manias and schizophrenic psychosis cause serious behavioural disturbances (Ustün et al. 1999). The majority of patients experience a chronic relapsing-remitting course of the disorders (Bromet and Fennig, 1999; Altamura et al. 2011).

5.1.2. Available therapies and unmet medical need

Antipsychotic medications are first-line medication treatment for schizophrenia. They have been shown in clinical trials to be effective in treating symptoms and behaviours associated with the disorder. Antipsychotic medications have significant side effects; assessment and management of these adverse effects are an important part of treatment.

Evidence-based psychosocial interventions in conjunction with pharmacotherapy can help patients achieve recovery (Stroup TS and Marder S. 2019, UptoDate).

The antipsychotic drugs used for the treatment of schizophrenia include quetiapine, clozapine, iloperidone, haloperidol, risperidone, paliperidone, ziprasidone, asenapine, lurasidone, aripiprazole and olanzapine. For uncooperative patients or patients who do not want to take oral antipsychotics injectable IM antipsychotics are available (e.g., haloperidol, olanzapine, aripiprazole, and ziprasidone) (Stroup and Marder 2019).

Treatment options for management of Bipolar disorder can be broadly classified as mood stabilizers (lithium, valproate, lamotrigine, carbamazepine/oxcarbazepine and topiramate), antidepressants and antipsychotic medications (e.g. olanzapine, quetiapine, aripiprazole, risperidone, paliperidone, amisulpiride, asenapine, ziprasidone and haloperidol) (Shah et al. 2017).

Pharmacologic treatment is considered the cornerstone of treatment for patients with schizophrenia and BP1. However, patients often fail to adhere to treatment, and this has a severe negative effect on prognosis in these kinds of mental health illnesses. Non-adherence is thought to raise the risk of psychotic relapse by a factor of three to five, and in schizophrenia is associated with rehospitalisation and poor quality of life with the risk of suicide nearly four times higher in service users who are poorly adherent Gibson et al. 2013). In bipolar disorder, there is a similar association with relapse, hospital admission and suicide (Clatworthy et al. 2007; Lage et al. 2009).

In order to improve adherence, reduce gaps in therapy, and prevent relapse compared with oral antipsychotics long-acting injectable (LAIs) antipsychotics were developed. The first LAIs, fluphenazine enanthate and decanoate, were introduced in the 1960s. Numerous LAI antipsychotics have been developed and marketed in the meantime. Aripiprazole 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.

Accurate information on a patient's medication adherence is of great clinical relevance in these patient populations. The drug-device product Abilify MyCite is intended to measure adherence over time, as the patient´s medication data over time is recorded and shared with the HCP. No such system or method for measurement of medication adherence is available within the EU.

5.1.3. Main clinical studies

As this is a "hybrid application", all clinical effects of the active substance aripiprazole are cross-referenced from the authorised reference product Abilify (EMEA/H/C/000471).

The submitted evidence to support the claimed indication "measurement of medication adherence" for Abilify MyCite comes from two open label, multicentre, single-arm, therapeutic exploratory trials of 8-weeks duration, studies 316-14-220 and 316-13-215.

The primary objective of **Study 316-14-220** was to investigate the usability of the MIND1 system (now: Abilify MyCite system) in patients with schizophrenia with regard to their ability to pair and apply the patch independently and successfully by the end of the Week 8 trial visit (as defined on a score 91 to 100 on a 100-point usability scale).

The primary objective of **Study 316-13-215** was to assess the functionality of an integrated call centre for the Digital Medicine System (DMS) (now: Abilify MyCite system) by adult subjects with SCH, BP1 or MDD, based on the frequency of their inbound and outbound calls.

5.2. Favourable effects

All clinical effects of the active substance aripiprazole are cross-referenced from the authorised reference product Abilify (EMEA/H/C/000471). Abilify is effective at treating symptoms of schizophrenia using standard rating scales (such as the Positive and Negative Syndrome Scale, PANSS) at treating manic episodes using standard measurements such as the Young-Mania Rating Scale (YMRS) scale (EPAR Abilify EMA/807076/2016). The use of aripiprazole is recommended in several evidence based guidelines (e.g. NICE).

- No relevant favourable effects of the Abilify MyCite System have been demonstrated. In study 316-14-220, 55.2% (37/67) of patients with schizophrenia were "able to pair and apply the patch of the drug-device system independently and successfully" by end of week 8, scoring 91 to 100 points on the SAUSS-HCP 100-point scale. 55 out of 67 patients (82.1%) were "able to pair and apply a patch successfully by the end of the Week 8 trial visit independently or with minimum assistance" (secondary endpoint).
- Study 316-13-215 investigated the functionality of an integrated call centre for the digital medicine system. In total, subjects made 136 inbound calls and received 257 outbound calls. The analysis of this data revealed that most of the inbound calls were due to pill status tile (37.5%) and issues with the patch (12.5%).

5.3. Uncertainties and limitations about favourable effects

At present, it is still not possible to conclude on the comparability of Abilify MyCite with Abilify tablets (without sensor) due to the many deficiencies of the in vitro dissolution tests, i.e. the bridge to the reference product remains questionable.

Both main clinical studies utilised previous versions of the Abilfy MyCite systems that differ remarkably from the drug-device system actually intended to be authorised. In both studies, previous versions of the Abilify MyCite system were utilised: two different versions of the **MIND1** system were used in study 316-12-220 and in study 316-13-215 **DMS** was used. The results obtained in both trials might thus not be applicable for the to-be marketed system. In addition, the usability and functionality of the whole actual drug-device system currently remains not assessable from the data provided.

There is no firm evidence from the two clinical studies to support the claim "to measure medication adherence" since the studies had primary objectives that did not investigate adherence.

The applicant seeks approval of Abilify MyCite in patients with schizophrenia and with bipolar I disorder. However, the studies included only patients, who were on a stable dose of aripiprazole and mostly "mildly ill" (concerning their mental health status), with low levels of cognitive impairment, willing and capable to use the system. In trial 316-13-215, there was also a pre-selection of "good performers" for the observation phase (only subjects with ≥ 50% patch wear during Week 2). The results may thus not be generalizable to a more typical population of patients with schizophrenia or BP1 (i.e. more severe or acutely ill patients, patients with high levels of delusional symptoms or patients with low illness insight). Therefore, the patient population proposed in the SmPC is considered too broad.

There is no information on how long Abilify MyCite should be used and when patients should be switched to Abilify tablets without sensor . It is also severely questioned, whether Abilify MyCite would be beneficial, for example, in patients with paranoia; in these patients, this system might even decrease adherence/ compliance.

In Study 316-14-220 patients received a 3-weeks training and even then, only slightly more than half of the patients were able to use the patch correctly after 8 weeks. However, subjects were assessed as being able to use the patch correctly, if they succeeded in doing so on only one visit during the 8 weeks trial duration. It needs to be further discussed how much training would be necessary to ensure correct use.

In both clinical studies, a call centre was set up to assist patients in using the drug-device system. The applicant plans to establish a call centre also in "real-life treatment", however, the exact mode of operation is not explained.

In the SmPC it is stated that Abilify MyCite can be taken with or without food. However, this information cannot be bridged easily from Abilify® to Abilify MyCite, as it remains unknown whether the detection of the signal from the sensor is influenced by the presence of food and if yes, to what extent. Possible effects of concomitant medications were also not studied.

5.4. Unfavourable effects

With the response to the D120 LoQ, the applicant submitted a table showing the differences between the used systems in the clinical trials and the to-be commercialized system. The to-be-marketed Abilify MyCite system (i.e. also the patch and consequently also the components of the adhesive material of its strip) differs considerably from the drug device systems used in both pivotal studies (see Section 3.3.5). Therefore, no clinical safety data with the new system are available.

In general, the amount of reported adverse events in the two clinical trials was low and in line with what is known for aripiprazole. 55.2% of the subjects in study 316-14-220 had an AE and 42.9% of the subjects in study 316-13-215 experienced an AE. The low number of AEs might be attributable to the reporting approach, which only occurred at the site visits and/or the short duration of the trials (8 weeks).

The adverse event profile of the active compound aripiprazole is listed in the PI of Abilify MyCite and corresponds with the adverse events listed for the reference product Abilify.

32.8% of the subjects in trial 316-14-220 and 42.9% of the subjects in trial 316-13-215 experienced device-associated TEAEs. All of these TEAEs were found to be patch-related. The most frequent device-associated TEAEs were rash, pruritus and erythema. The possible occurrence of skin related TEAEs is reflected in the PI of Abilify MyCite. Therefore, compared with Abilify tablets without device, Abilify MyCite poses an additional risk of device-associated TEAEs. In some cases, these patch-related events even led to the discontinuation from the trial. In total, five patients had to discontinue due to patch related events.

Abilify MyCite is also considered to pose the risk of overdosing/taking extra doses: In study 316-14-220 it was reported that 6 out of 67 subjects took an overdose. Taking an overdose or more than one tablet as prescribed increases the risk of side effects or of interactions with concomitantly taken medications. The applicant agreed with this conclusion and included overdose in certain situations of device malfunction in the list of safety concerns as an important potential risk.

In Study 316-14-220, 93.2% of the IEMs of the placebo + IEM tablets (which the patients took under supervision of the trial staff) were registered. When looking at the proportion of ingested (vs expected) aripiprazole + IEM tablets only 59.4% (1824/3072) across all expected ingestion days during the trial were registered. Thus, the system does not have a detection accuracy of nearly 100% even under supervised conditions. This concern is further supported by the results of the IEM activation testing, which not only revealed a great variability of the life-spans of the IEMs, but also showed that some of the IEMs exhibited no life-time at all. Any missed or delayed detection of the ingestible sensor signal due to poor connectivity, poor patch coverage, sensor not working properly, etc. could potentially lead to a patient taking an additional dose.

5.5. Uncertainties and limitations about unfavourable effects

The overall safety database for the drug-device combination is small. The two main clinical studies 316-14-220 and 316-13-215 had a duration of 8 weeks respectively and the mean duration of exposure to the different versions of the Abilify MyCite system was about 47 days in both trials. The short duration of the trials hampers a long-term safety assessment. As the intended duration of use is not stated in the proposed SmPC, no conclusion on the adequacy of the safety database is possible.

In addition, it remains uncertain how applicable the obtained results for the to-be marketed system are, as it turned out that the to-be-marketed Abilify MyCite system, including its patch, differs considerably from the drug device systems used in both pivotal studies and in all other studies conducted during the clinical development program.

Several uncertainties with regard to potential overdosing came up. Upon request, the applicant outlined that multiple extrinsic (e.g. poor skin contact of the patch, poor Bluetooth connectivity etc.) and intrinsic factors (user errors) may contribute to a missed or delayed detection of the IEM signal by the smartphone app and included overdose as an important potential risk.

Uncertainties arise also concerning the usability of the patch. The mean patch wear time was short in both clinical studies and the reasons for outbound calls in study 316-13-215 indicated that nearly all

subjects faced issues with applying, wearing, and/or changing the patch. The patch can provoke skin and subcutaneous tissue disorders. In addition, there were no clinical safety data presented for the to-be-commercialized Abilify MyCite system, which among other uncertainties also comprises a different patch than used in the clinical trials.

5.6. Effects Table

Table 23: Effects Table for Abilify MyCite for the claimed indication of measuring medication adherence in adult patients with schizophrenia and bipolar disorder 1.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects*						
Effective treatment for patients with SCH or BP1			Aripiprazole		No evidence as no conclusion on the comparability between Abilify and Abilify MyCite is possible	*In vitro* dissolution testings
Measurement of medication adherence			Abilify MyCite	none	No confirmatory evidence	(1) (2)
Unfavourable Effects of Abilify MyCite*						
Rash	Incidence of rash	% of patients	4.5	none	High: The patch provokes skin and subcutaneous tissue disorders.	(1)
		%	22.4	none		(2)
Pruritus	Incidence of pruritus	%	13.4	none		(1)
		%	4.1	none		(2)
Erythema	Incidence of erythema	%	6.0	none		(1)
		%	4.1	none		(2)
Skin irritation	Incidence of skin irritations	%	1.5	none		(1)
		%	2.0	none		(2)
Dermatitis contact	Incidence of cont. dermatitis	%	4.5	none		(1)
Rash erythematous	Incidence of rash erythematous	%	3.0	none		(1)
Blister	Incidence of blister	%	1.5	none		(1)
Rash papular	Incidence of papular rash	%	1.5	none		(1)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Overdose/Extra dose	Patients taking an overdose/extra dose	Patients	6	none		(1)

Abbreviations:
Notes: (1) Data from trial 316-14-220; (2) Data from trial 316-13-215
* The well-known favourable/unfavourable effects of aripiprazole (Abilify) are not depicted in the table above.

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

Abilify MyCite contains the active substance aripiprazole. Aripiprazole is an antipsychotic medicine, recommended in international guidelines (e.g. WHO, NICE) as an option for the treatment of schizophrenia and BP1 disorder. Abilify is effective at reducing symptoms of schizophrenia and at treating and preventing high moods in patients with bipolar I disorder.

Adherence to medication is crucial for treatment success in patients with Schizophrenia or BP1. However, non-adherence is a serious and well-recognised problem in these patient populations. Adherence to oral drug treatment can be measured by subjective methods, such as self-report and physician report, or objective methods, such as pill counting, blood or urine analysis, and electronic refill records. However, these methods have limitations and so far, no method is available that allows daily monitoring of dosing, and thus, a reliable and precise daily measurement of medication intake/drug adherence. There is an unmet medical need to improve medication adherence in these psychiatric patients; providing patients, caregivers, and physicians with adherence data could be valuable for making better informed treatment decisions.

However, the data to support various aspects of the application including the claimed indication is insufficient:

Based on *in vitro* comparability studies, bioequivalence between Abilify MyCite and its reference product Abilify has not been demonstrated; this is however needed to build a bridge to the reference product, in line with the legal basis of this hybrid application.

A beneficial effect of Abilify MyCite with regard to measurement of medication adherence was not demonstrated in the submitted clinical studies since they were not designed to investigate this; only limited aspects of usability and technical performance were studied.

The target population, for which this drug-device system could be beneficial, has not yet been defined. The applicant applies for an indication in adult patients with SCH or BP1 disorder (similar to Abilify, but excluding adolescents), which is considered too broad. In both clinical studies, only patients who were "mildly ill", who had low levels of cognitive impairment, were capable and willing to use the system and were already on a stable dose of aripiprazole were included. From the results of both studies, it can be concluded that using the system is rather complicated. It is doubtful that patients who are acutely or more severely ill, with significant cognitive impairment, low illness insight or high intensity of delusional symptoms and suspiciousness could be targeted.

In addition, the overall functionality of the system to reliable register medication intake is questionable. For this purpose, a detection accuracy of nearly 100% would be necessary. However, the in vitro (IEM activation tests) and in vivo data (from the main clinical studies) shows that registration

of the IEM tablet might be delayed (measurement of real-time intake is not possible) or not occur at all. If the detection of the tablet is delayed or does not occur, the risk of overdosing/ taking extra doses needs to be considered. Taking extra doses and overdosing are an important potential risk that has been included in the RMP.

Beside the established safety profile of aripiprazole, the most important unfavourable effects of the Abilify MyCite system are skin- and subcutaneous tissue disorders originating from patch wearing. This finding was highly consistent in both clinical trials; it poses an additional risk compared with the use of the aripiprazole tablets without device. Some subjects even had to discontinue the trial due to the emergence of patch related adverse events (rash, erythema, pruritus, papular rash and pruritic rash), implying that a substantial amount of patients might not be able to use the Abilify MyCite system.

There is potential risk for lower trust in the treating psychiatrist asking a patient to be monitored, and this might even result in lack of adherence to treatment. A good relationship with the treating psychiatrist is built over a long time and a careful treatment plan jointly agreed between the HCP and patient cannot be replaced by a digital system.

Importantly, neither clinical efficacy nor safety data have been generated with the Abilify MyCite system intended to be authorized.

5.7.2. Balance of benefits and risks

Abilify MyCite is a novel diagnostic tool, the first of its kind in the EU, to digitally track (date and time) oral aripiprazole ingestion in patients. Provided that the system works properly and is used correctly, dosing can be monitored and thus, adherence to medication can be measured (claimed indication) by patients themselves, as well as by their physicians, caregivers or even family members.

Concerning *efficacy*, both clinical studies included in the dossier fail to provide a solid basis of evidence for the claimed indication as the study objectives only relate to limited aspects of usability and technical performance. Potential benefits in terms of adherence measurement, patient management and resulting impact on clinical outcomes - as claimed by the applicant - are not reflected in the study objectives and related endpoints.

Concerning *safety*, device-associated TEAEs related to the use of the patch (rash, pruritus and erythema) were observed in the studies that even led to study discontinuation in some cases. The occurrence of these patch related skin reactions poses an additional risk compared with Abilify tablets without sensor. Furthermore, for the patch intended to be marketed no clinical safety data is available at all.

Currently it is not possible to conclude on the reliability of sensor detection or sensor signalling. Any missed or delayed detection of the ingestible sensor signal due to poor connectivity, poor patch coverage, sensor not working properly, etc., could potentially lead a patient to take an additional dose, and therefore bears the potential of overdosing.

In conclusion, the benefit/risk balance is negative as no clear treatment benefit can be identified to outweigh the risks of the Abilify MyCite System as outlined above.

5.7.3. Additional considerations on the benefit-risk balance

N/A

5.8. Conclusions

The overall B/R balance of Abilify MyCite is presently negative.

6. Literature References

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