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- **Document title: A Multicentre, 8-week, Single-aim, Open-label, Pragmatic Trial to Explore Acceptance and Perfonnance of Using a Digital Medicine System with Healthcare Professionals and Adult Subjects with Schizophrenia, Schizoaffective Disorder, or First Episode Psychosis on an Oral Atypical Antipsychotic (Aripiprazole, Olanzapine, Quetiapine, or Risperidone)**
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Otsuka Pharmaceutical
Development and Commercialization, Inc

Medical Device

OPC-14597 Digital

CLINICAL PROTOCOL

A Multicentre, 8-week, Single-arm, Open-label, Pragmatic Trial to Explore Acceptance and Performance of Using a Digital Medicine System with Healthcare Professionals and Adult Subjects with Schizophrenia, Schizoaffective Disorder, or First Episode Psychosis on an Oral Atypical Antipsychotic (Aripiprazole, Olanzapine, Quetiapine, or Risperidone)

Protocol No. 031-201-00186

EudraCT No. 2017-004602-17

CONFIDENTIAL – PROPRIETARY INFORMATION

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Protocol 031-201-00186

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Protocol 031-201-00186

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development and Commercialization, Inc Name of Investigational Medicinal Product: Medical Device (OPC-14597 Digital)	Protocol No.: 031-201-00186 EudraCT No.: 2017-004602-17
Protocol Title:	A Multicentre, 8-week, Single-arm, Open-label, Pragmatic Trial to Explore Acceptance and Performance of Using a Digital Medicine System with Healthcare Professionals and Adult Subjects with Schizophrenia, Schizoaffective Disorder, or First Episode Psychosis on an Oral Atypical Antipsychotic (Aripiprazole, Olanzapine, Quetiapine, or Risperidone)
Clinical Phase:	4
Treatment Indication:	Schizophrenia
Objective(s):	Explore the acceptance and performance of the digital medicine system (DMS) with healthcare professionals (HCPs) and adult subjects with schizophrenia (SCH), schizoaffective disorder, or first episode psychosis.
Trial Design:	This is a multicentre, 8-week, single-arm, open-label, pragmatic trial to explore the acceptance and performance of using the DMS with HCPs and adult subjects with SCH, schizoaffective disorder, or first episode psychosis on an oral atypical antipsychotic (aripiprazole, olanzapine, quetiapine, or risperidone). The DMS includes a drug-device combination of a CoEncapsulated (CoE) product (approved antipsychotic medication enclosed with an Ingestible Sensor Pill (Ingestible Sensor Pill is also called as a miniature ingestible event marker [IEM] in tablet [MIT]), a patch (Wearable Sensor), and an application software to convey level of activity and rest, and to mark events through the act of ingestion. Subjects in this trial will receive an initial introduction to the DMS, and have HCP visits at screening/baseline, Week 4, Week 8/early termination (ET), and as directed by the HCP for the duration of the subject's participation in the trial. The HCPs will have access to a digital medicine (DM) dashboard where notifications can be setup around medication ingestion.

	Screening/Baseline Visit (Days -7 to -1) After providing the informed consent, subjects will enter the screening period for up to 1 week (7 days). Screening and baseline may occur at a single visit or may occur over 2 visits up to 7 days apart. The screening period may be extended at the discretion of the HCP. Subjects will be between 18 and 65 years of age, inclusive, at the time of screening/baseline visit with a confirmed clinical diagnosis of SCH or schizoaffective disorder (defined by International Classification of Disease [ICD]-10 codes F20 and F25), or first episode psychosis using case note review. Subjects entering the trial will be treated with one of the oral atypical antipsychotics defined in the trial. The treatment medication decision will be determined by the HCPs and independent from the protocol. Assessment Period (8 Weeks): Initiation of the DMS will commence at the baseline visit, with subjects ingesting the CoE product, wearing the patch, and using the smartphone application (app) for a total of 8 weeks during the assessment period from baseline visit to Week 8 visit. During the assessment period from baseline visit to Week 8/ET visit: • Subjects will visit the HCP for clinical evaluations at Week 4; • Subjects will collect their DMS prescription refill at Week 4 visit for next 4 weeks until Week 8/ET visit; • Subjects will visit the HCP at Week 8/ET and undergo another clinical evaluation. Safety and tolerability data will be collected and evaluated on an ongoing basis, as assessed by the frequency and severity of serious adverse events (SAEs), and device-related nonserious adverse events (AEs). Subjects will be monitored on the technology by the HCPs, who will review the HCP dashboard data at a minimum of every 2 weeks and make changes to current treatment plan and therapy at their discretion. The HCPs may request that a subject return to the site for unscheduled visits as deemed appropriate. In the event of an unscheduled visit, review of the DMS dashboard and safety events will be collected.

	Follow-up: Week 8/ET visit evaluations will be completed for any subject withdrawn from the trial at any time (for any reason other than full withdrawal of the consent). Following the Week 8/ET visit, the subjects will not use the DMS and return to standard care (routine follow-up from care teams and continue non-DM medications). Subjects will have access to their trial account or data in the smartphone app up until 30 days after the last subject's Week 8/ET visit. After this duration, the subjects will no longer have access to their data via the smartphone app. A safety follow-up phone call will occur at 2 weeks after the Week 8/ET visit, which will be the last official subject contact. Healthcare Utilisation Record Evaluation: Twenty-four weeks before and after the baseline visit (for a total of 48 weeks), all hospital admissions (psychiatric and non-psychiatric) would be recorded and assessed as either 'planned' or 'unplanned' and 'related' or 'unrelated' to the psychiatric illness. Similarly, all encounters between any HCP (psychiatric and non-psychiatric) and the subject will be recorded to obtain the following information: • The nature of the contact (eg, home visit, inpatient, outpatient, HCP visit, day centre); • The HCP role (eg, community psychiatric nurse); • Whether the contact was planned or not; • Whether or not the contact was initiated as a result of data from the DMS; • Any medication titration, adherence counseling, education, and lifestyle coaching. This data will be reported in the data collection tool at Week 24 (or up to 7 days after this time point).

Subject Population:	The trial will enrol approximately 60 male and female adult subjects between 18 and 65 years of age, inclusive, with a confirmed clinical diagnosis of SCH or schizoaffective disorder (defined by ICD-10 codes F20 and F25), or first episode psychosis who are prescribed either aripiprazole, olanzapine, quetiapine, or risperidone. There is no limit on the duration of illness for those with SCH or schizoaffective disorder but first episode psychosis is defined as less than 3 years since presentation to the mental health team or first antipsychotic prescription.
Inclusion/Exclusion Criteria:	<u>Key Inclusion Criteria:</u> 1) Subject must be willing and able to give written (signed and dated) informed consent, which includes adherence to trial requirements and restrictions before enroling in the trial. Subject must be willing to adhere to trial procedures, including troubleshooting of the DMS by a third party if needed. 2) Subject must be able to read and understand English. 3) Male and female subjects 18 to 65 years of age, inclusive, at the time of informed consent. 4) Subject possessing their own smartphone or a smartphone provided by the Sponsor, and being familiar with its use and willing to download and interact with the DMS app, completing all tasks as well as adequately operate all devices, as applicable. Caregiver/support person or other third party assistance can be utilised, if needed, although all subjects should be encouraged to attempt all tasks themselves. 5) Subject possesses the capacity to utilise the technology interfaces (eg, open and navigate software applications using the touch screen) and telephone features of a smartphone. The subject has satisfactory mobile phone reception (preferably 3 bars or more, or have Wi-Fi) at home and/or at work for trial-designated wireless carrier. 6) Subject is cooperative, able to ingest oral medication, willing to complete all aspects of trial, and capable of reporting AEs. 7) Clinical diagnosis of SCH or schizoaffective disorder (defined by ICD-10 codes F20 and F25) or first episode psychosis using case note review. 8) Subjects prescribed aripiprazole, olanzapine, quetiapine, or risperidone.

9) Subject must fulfill at least one or more of the following:
   - Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team;
   - Referral to an acute intervention team, prior to any hospital admission;
   - Referral from an acute intervention team to a community team;
   - Managed by community services (inclusive of patients on Care Programme Approach);
   - Inclusion within early intervention caseload (< 3 years from initial symptoms);
   - HCP determines the subject would benefit from using DMS.
10) Subject's general medical condition such that participation in the trial does not pose any additional risk as per HCP's judgment.
11) Skin on the anterior chest just above the lower edge of the rib cage that is free of any dermatological problems (eg, dermatosis or dermatitis, open wounds, or other skin disorders such as warts, rashes, atopic dermatitis, or irritations).

Key Exclusion Criteria:

1) Subject with any disorder including but not limited to intellectual developmental delay or disorder, major neurocognitive disorder or other condition that may impact the subject's ability to participate in the trial or interact with the smartphone app.
2) Subject who is likely to be incapable of using the DMS technology, even with assistance.
3) Subject who has a history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere with assessments of safety or usability during the course of the trial, including but not limited to, hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the HCP.
4) Subject with a known allergy to adhesive tape or any pertinent components of the patch or CoE product.
5) Prisoner must not be enroled into this trial.

	6) Subject who is hospitalised due to mental or physical illness (inpatient) at the time of screening/baseline must not be enroled into this trial. 7) Any subject who, in the opinion of the HCP, should not participate in the trial. 8) Any subject who, through religious or lifestyle choices, will not take gelatin capsules. 9) Female (females of childbearing potential [FOCBP]) who are breast-feeding and/or who have a positive pregnancy test result prior to receiving trial enrolment, or who plans to become pregnant during the trial.
Trial Site(s):	Approximately 4 sites in the United Kingdom.
Device, Dose, Dosage Regimen, Treatment Period, Formulation, Mode of Administration:	The DMS consists of a: • CoE product which contains an approved antipsychotic medication enclosed with an Ingestible Sensor Pill (Ingestible Sensor Pill is also referred as an MIT); • Compatible medical device, which is the Proteus Patch and Proteus® Medical Device Data Systems (MDDS). These are collectively referred to as the Patch + MDDS. Data received from the Proteus Patch is processed in the Patch Analytics Block and is transferred to the Proteus MDDS, both of which reside on the paired mobile computing device (eg, smartphone or tablet computer); and • Otsuka Medical Software, which has the following software components: 1) Otsuka Patient Component, which resides on the paired mobile computing device and receives data from the Proteus MDDS; 2) Otsuka Cloud-based Server; 3) Otsuka Healthcare Provider Web Portal; 4) Otsuka Caregiver Web Portal. The CoE product contains MIT and drug originator tablet of either aripiprazole, olanzapine, quetiapine, or risperidone (known as DM-Aripiprazole, DM-Olanzapine, DM-Quetiapine, or DM-Risperidone within the smartphone app). The treatment medication decision will be determined by the

	HCPs and independent from the protocol.

Trial Assessments:	**Acceptance and Performance**:
	• Using feedback from subjects, HCPs, and caregivers/support person on the use of the DMS:
	  • Subject Usability and Satisfaction Scale;
	  • HCP Utility Survey;
	  • Caregiver/Support Person Involvement Scale (if applicable).
	• Additional variables to better understand outcomes that may impact use of the DMS or be impacted by the use of the DMS:
	  • Patient Activation Measure-Mental Health (PAM-MH);
	  • Clinical Global Impression-Severity of Illness Scale (CGI-S).
	
	Safety: Safety will be assessed by SAEs, device-related nonserious AEs, and suicidality assessment.

Criteria for Evaluation:	**Primary Endpoint:** The primary endpoint is the proportion of days with good patch coverage during the trial, which will be calculated by the number of days with good patch coverage divided by the total number of trial days for each subject. The good patch coverage is defined as having at least 80% patch data available or MITs detected within the 24-hour period for each day while the subject is on the trial. **Secondary Endpoint:** The secondary endpoint is subject's adherence metric, which is the proportion of detected MITs over the expected MITs ingested during the trial days with good patch coverage. **Exploratory Endpoints:** 1) To explore the acceptance and performance of the DMS with HCPs and adult subjects with SCH, schizoaffective disorder, or first episode psychosis as measured by: • The proportion of time during the trial period when the subject wears their patch.

	• The engagement and satisfaction of subjects, HCPs, and caregivers/support persons (if applicable), as determined by surveys (Subject Usability and Satisfaction Scale, HCP Utility Survey, and Caregiver/Support Person Involvement Scale [if applicable]). • The proportion of days subjects are using the application and the proportion of days that investigators are using the HCP dashboard during the trial. • The proportion of ingested MITs registered on the digital health data server versus expected MITs ingested. 2) Additional variables will be captured to better understand outcomes that may impact use of the DMS or be impacted by the use of the DMS including: • Change from baseline to Week 8 in CGI-S; • HCP visits and associated setting of care; • Details surrounding any hospitalisations; • Occurrence and timing of community/home visits; • Any referrals during the observation period. **Safety Variables:** • Evaluate the safety and tolerability of the DMS, as assessed by the frequency and severity of SAEs, and device-related nonserious AEs; • Evaluate any product quality complaints that arise.
Statistical Methods:	The analysis will be conducted based on the intent-to-treat sample (ie, all subjects who enter the trial and use the DMS). Descriptive statistics will be provided for all primary, secondary, and exploratory endpoints and safety variables in general. Continuous variables will be summarised by tabulations of mean, median, range, and standard deviation. Tabulations of frequency distributions will be provided for categorical variables.

Trial Duration:	The total trial duration per subject from screening to the end of healthcare utilisation record evaluation will be up to 25 weeks.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
A and E	Accident and emergency
app	(smartphone or mobile) application
BP	Bipolar disorder
BP 1	Bipolar 1 disorder
BSI	The British Standards Institute
CE	Conformité Européene
CGI-S	Clinical Global Impression-Severity of Illness Scale
CI	Confidence interval
CoE	CoEncapsulated
CRIS	Clinical Interactive Record Search
DILI	Drug-Induced Liver Injury
DM	Digital medicine
DMS	Digital medicine system
DW5	Disposable Wearable Sensor Version 5
EHR	Electronic health record
ET	Early termination
EU	European Union
EudraCT	European Clinical Trial Data Base
FDA	(United States) Food and Drug Administration
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
HCP	Healthcare professional
IB	Investigator's Brochure
ICD	International Classification of Disease
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent ethics committee
IEM	Ingestible event marker
IRE	Immediately reportable event
ITT	Intent-to-treat
MAA	Marketing authorisation application
MDD	Major depressive disorder
MDDS	Medical Device Data Systems
MHA	Mental Health Act
MIT	Miniature IEM in tablet
MRP	Mutual Recognition Procedure
OPC	Otsuka Pharmaceutical Co.

OPDC	Otsuka Pharmaceutical Development and Commercialization, Inc
OPEL	Otsuka Pharmaceutical Europe Ltd.
PAM-MH	Patient Activation Measure-Mental Health
PQC	Product Quality Complaint
PSP	Personal and Social Performance Scale
SAE	Serious adverse event
SCH	Schizophrenia
SD	Standard deviation
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
UADE	Unanticipated adverse device effects
ULN	Upper limit of normal
US or USA	United States or United States of America

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1 Introduction

The digital medicine system (DMS) has been designed to assist individuals with the management of their daily health, wellness, and medication use.

The DMS is being developed as a healthcare management tool to objectively and precisely measure medication adherence, and to potentially enhance adherence. This advancement in the treatment of mental health patients will enable healthcare professionals (HCPs) to assess suboptimal adherence and make more informed treatment decisions. In addition, the DMS will provide a platform for engagement between subjects, HCPs, and caregivers/support persons.

The feasibility and validity of patient assessment (ie, completion of electronic questionnaires) using personal digital assistant or Palm handheld computers has been demonstrated in diverse schizophrenia (SCH) samples including hospitalised inpatients,[1] outpatients[2] and patients exhibiting high levels of paranoia.[3] For short trials of approximately 1 week, compliance rates with device and assessments have been promising, ranging from 87% to 97.7%[4,5] and subjects have rated the experiences positively.[4] Furthermore, SCH patients have reported a willingness to complete mobile phone assessments for 5 weeks or longer.[6] However, a more common observation in eHealth trials is large attrition curves (ie, a substantial proportion of participants drop out before completion or stop using the application).[7] In one of the longest mobile phone trials in SCH, approximately 20% of subjects did not complete the 12-week intervention and these “non-completer” subjects were characterized, as compared with “completer” subjects, by certain characteristics including lower self-reported living skills, more severe negative symptoms as measured by the Positive and Negative Syndrome Scale, and lower estimated premorbid verbal intelligence score as measured by the American National Adult Reading Test.[2]

Usability testing is key to the development process of mobile applications (app) and ensures the technology is understandable, attractive, and usable for the targeted patient population. However, outside of one-time laboratory settings, an additional challenge is demonstrating that a technology system is usable in the real-world environment for patients and across time. Although there have been a number of mobile phone trials in SCH, the DMS is a 3-part system which can measure medication adherence if subjects successfully engage in a number of processes across the 8-week trial.

The DMS is composed of:

- An approved antipsychotic medication enclosed with an Ingestible Sensor Pill which is otherwise also referred to in this document as CoEncapsulated (CoE) product. Ingestible Sensor Pill is also referred to as a miniature ingestible event marker (IEM) [from Proteus Digital Health Inc. (Proteus Ingestible Sensor™)] in a tablet (MIT);
- Compatible medical device, which is the Proteus Patch (Wearable Sensor) and Proteus® Medical Device Data Systems (MDDS). These are collectively referred to as the Patch + MDDS. Data received from the Proteus Patch is processed in the Patch Analytics Block and is transferred to the Proteus MDDS, both of which reside on the paired mobile computing device (eg, smartphone or tablet computer); and
- Otsuka Medical Software, which has the following software components:
  - Otsuka Patient Component, which resides on the paired mobile computing device and receives data from the Proteus MDDS;
  - Otsuka Cloud-based Server;
  - Otsuka Healthcare Provider Web Portal;
  - Otsuka Caregiver Web Portal.

The CoE product comprises a MIT and a drug originator tablet. The MIT includes an embedded IEM (also known as the Proteus Ingestible Sensor). The drug originator tablet is an approved antipsychotic medication of either aripiprazole, olanzapine, quetiapine, or risperidone, which will be also known as digital medicine (DM)-Aripiprazole, DM-Olanzapine, DM-Quetiapine or DM-Risperidone within the smartphone application (app).

The subject worn patch measures physical parameters, such as activity and rest, as well as a time stamp of when the atypical antipsychotic medication combined with an ingestion sensor are taken. This data is transferred from the patch to the subjects' smartphone and to a secure cloud-based server.

The subject can view the time of tablet ingestion each day (or missed/multiple doses) together with their daily duration of rest and activity and manually enter their current mood and quality of rest. In addition, the subject's selected HCPs and selected caregivers/support persons can view this information via the cloud-based server with appropriate subject's consent. HCPs can set up missed dose notifications to monitor any lapses in subject's adherence.

The first DMS product (Abilify MyCite®) is approved by the United States (US) Food and Drug Administration (FDA).

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Background

Poor adherence to medication is a well-recognized problem in psychiatric patients that can be improved to varying degrees by planned interventions, such as medication monitoring.[8] A variety of treatment models have been developed to improve management of patients in general and medication adherence in particular. These methods include therapeutic drug monitoring and medication event monitoring, among others. Despite availability of these types of management systems, poor medication adherence remains a major barrier to achieving optimal health. Current medical event monitoring devices do not provide a reliable proxy for actual medication ingestion, and therapeutic drug monitoring may be invasive and expensive for routine clinical use.

Several studies have shown that patients with severe mental illness have interest in managing their physical and mental health care through digital technologies such as smartphones. A meta-analysis of cross-sectional studies involving people with psychosis (n = 2129) showed the extent of adopting digital technology. In this trial, 66% of patients owned a mobile device with 57% on average using the device daily. When patients with psychotic disorders (n = 1172) were questioned regarding utility of the device, tracking and monitoring their mental health (60%), receiving information about their physical or mental health (56%), reminders about taking their medication (56%), and facilitating patient contact with health professionals (51%) were top reasons cited for engagement with a mobile device.[9] Additional studies showed that patients diagnosed with SCH were willing to use electronic devices daily to complete electronic questionnaires in both hospitalised and outpatient setting.[1,10] Further, another trial noted that patients found engagement for self-monitoring and self-report of activity to be non-stigmatizing and easy to integrate into their daily lives.[11]

Otsuka Pharmaceutical Company Ltd. (Otsuka) is developing a combination drug-device consisting of CoE product. The antipsychotic medication which will be used in the trial will be either aripiprazole, olanzapine, quetiapine, or risperidone (see Section 1.3.1).

An earlier version of this 3-part system has been examined in a 4-week observational trial with 12 bipolar disorder (BP) and 16 SCH subjects with weekly site visits.[12] However, the extent of weekly face-to-face support/training necessary for patients to successfully use this 3-part system across a longer period is unknown. Further, other support factors such as caregiver/support person involvement or integrated call centre availability were not reported and may be important in supporting ongoing usability of the system. Self-reported usability and acceptability ratings from patient and HCPs are also important in

demonstrating that the system is usable in its entirety. Finally, it is important to know if there are patient characteristics which predict patient competence and willingness to use the system. Such data will help identify patients who can successfully use the DMS, and provide information to the sponsor about the specific enhancement of the device or support services which could help to extend the range of patient users.

Ingestible Event Marker

The IEM is a Conformité Européene (CE)-marked class IIa medical device (CE 559373) indicated to time stamp, via ingestion, any discrete event. The IEM communicates medication ingestion to a compatible medical device, such as the Wearable Sensor (or Proteus Patch), CE-marked class IIa medical device (in 2010 by The British Standards Institute (BSI), Proteus Digital Health's European Union [EU] notified body). This information, along with additional physiologic data, is processed, displayed, and stored on the subject's compatible computing device, and made available to the subject's HCP.

Proteus's IEM is approved for marketing in the EU and in the United States (US) as a medical device.

The entire information chain from IEM to compatible medical device is part of the DMS, as depicted in Figure 1-1.

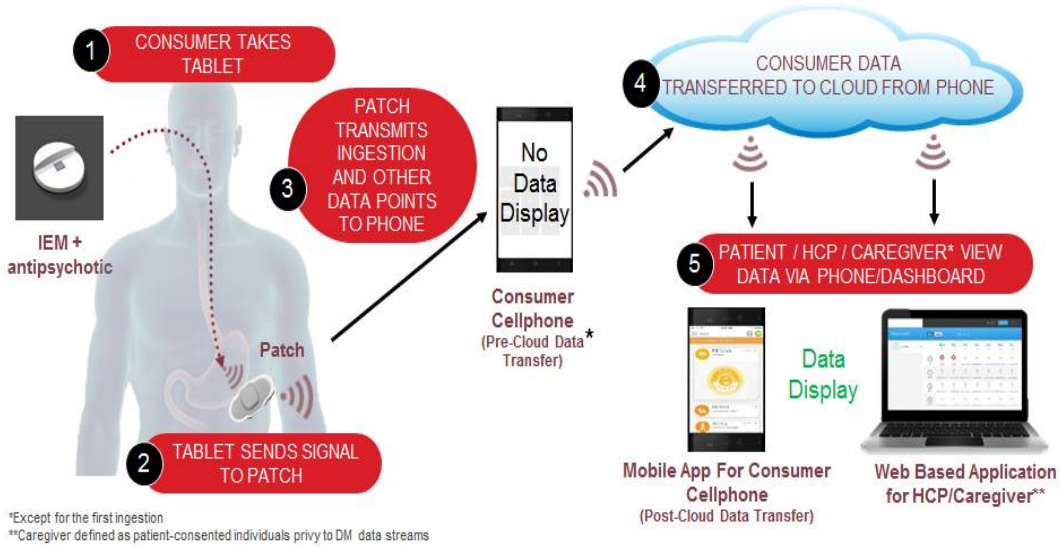

Figure 1-1 Digital Medicine System: Antipsychotic Medication with Ingestible Event Marker and Compatible Medical Device

The rationale for developing the DMS is to integrate a clinically important behavioural diagnostic capability into treatment that will quantify subject medication ingestion in a manner functionally equivalent to direct observation, with the goal of improving management and compliance of subjects who are at risk of worsening disease. The overall clinical development plan is to demonstrate the ability of the DMS to safely measure medication adherence in subjects, improve outcomes, and provide HCPs with adherence data to make better informed treatment decisions.

1.1 Nonclinical Data

Please refer to the Investigator's Brochure (IB) for more detailed information regarding nonclinical data.[13]

1.2 Clinical Data

A prototype of a digital health feedback system has been studied previously in subjects with bipolar disorder and SCH by Proteus Digital Health, Inc. In that 4-week observational trial, 12 bipolar and 16 SCH adult subjects utilised a networked system to electronically confirm ingestions of oral medications using ingestible markers. All subjects were on a stable regimen of oral medication and wore a Wearable Sensor (version RP2 and also called a Patch) and co-ingested one placebo + 2 IEM-Tablet assemblies (each consisting of a placebo tablet having one Ingestible Sensor affixed to one of the tablet's surfaces) with every ingestion of prescribed medication. Upon ingestion, each marker was activated by stomach fluid electrolytes and communicated a unique identification (ID) to an adhesive Wearable Sensor (version RP2 and also called a Patch) that logged the marker's ingestion date and time. The Wearable Sensor also collected biometrics, and periodically transferred its stored data via a smartphone to a password-protected server using secure encryptions. Subjects and caregivers/support person, if designated by each subject, were able to view collected data on a dedicated website. No interventions were planned based upon the collected data.

Twenty-seven subjects (96%) completed the trial. Mean taking adherence was 74% (95% confidence interval [CI]: 64, 84%) and 67% (95% CI: 55, 79%) of doses were taken within 4 hours of the prescribed dosing time. Activity consisted of 845 to 15930 steps daily and sleep ranged from 3.2 to 15.2 hours daily. For individual subjects, average sleep disruption was as low as 5% and as high 43% for the entire trial period. Minor skin irritation occurred at the site of the adhesive Wearable Sensor in 5 subjects (18%). No adverse events (AEs) occurred from the ingestion marker. No subject developed paranoid

ideation while using the system. The majority of subjects regarded the DMS favorably and believed that it could be useful in the management of their health.

In addition, the following clinical trials evaluating components of the DMS have been conducted by Otsuka.

Trial 316-13-205 was an open-label, phase 1 trial conducted to evaluate the skin irritation potential for, and adhesion to the skin of, the RP4 patch from Proteus Digital Health Inc. This trial was conducted as an investigational new drug or investigational device exemption trial. This trial used a cumulative skin irritation patch test (modified Draize scale) to determine the total cumulative and mean skin irritation scores for the RP4 patch. The total and mean adhesion scores were also determined. The overall safety and tolerability of the patch were evaluated.

Approximately 30 healthy males and nonpregnant females, 18 to 45 years of age, were randomly assigned in a 1:1 ratio (once screening was completed and the subject was deemed eligible to participate in this trial) to receive the RP4 patch on either the right or left side of the body, just above the lower edge of the rib cage. The same location on the opposite side was used for application of the control patch (Webril™ pad attached to a nonporous, plastic film adhesive bandage). The subjects were to wear the RP4 patch and the control patch for 7 days, at which time a new RP4 patch and control patch were applied; this was to be repeated an additional 3 times for a total wear duration of 28 days.

Skin irritation scores were determined for the RP4 patch and control patch sites before the initial application, and 30 minutes after removal of the patches following each 7-day wear period. Adhesion scores were collected 1 hour after the initial application of the patches and before they were removed following each 7-day wear period. Overall, there were no erythema or edema AEs noted for either the RP4 patch or the control patch. The adhesiveness of the RP4 patch was similar to that observed for the control patch.

Please refer to the IB for more detailed information.[13]

Trial 316-13-204 was a phase 4, exploratory, open-label, single-arm, observational investigational device exemption trial to obtain feedback from the subject and caregiver/support person (if applicable) about the use of the DM prototype and any application (ie, software) updates that were made during the trial. The trial was conducted at 2 research sites and was designed to include approximately 45 male and female subjects, 18 years of age or older, with a current diagnosis of bipolar 1 disorder (BP 1) or major depressive disorder (MDD), according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, who were deemed stable by the clinical

investigator (eg, symptoms and medication) for a period of 3 months before enroling in the trial. Subjects were enroled in 2 cohorts consisting of 35 subjects with BP1 and 23 subjects with MDD, who were in the stable phase of their disease. Subjects wore a patch and co-ingested one placebo + IEM tablet with every ingestion of prescribed medication, which may have been once daily or at multiple times of the day, depending on the subject's prescribed dosing regimen for 16 weeks.

At the last trial visit, 88.2% of the subjects agreed that the Otsuka application was easy to use, and 68.6% of subjects felt it was comfortable to wear the patch. In addition, 74.5% of subjects and 78.6% of caregivers reported that they felt satisfied with the DMS, and 74.5% of subjects and 72.0% of caregivers reported they would be interested in using the DMS in the future. There were no unanticipated adverse device effects (UADEs) reported during the trial.

Trial 316-13-206a was a phase 4, exploratory substudy in 30 healthy male and nonpregnant female subjects 18 to 65 years of age and this was the first trial for a subject to ingest a tablet where the IEM was embedded in the aripiprazole. The objective was to measure the accuracy of the IEM detection by the DMS and the latency period between ingestion after fasting and after a high-fat meal, and detection. The subjects ingested one IEM tablet approximately every 2 hours for a total of 4 ingestions. The subjects ingested one 10-mg aripiprazole + IEM tablet without food (hour 0), one placebo + IEM tablet without food (approximately hour 2), one placebo + IEM tablet with a high-fat meal (approximately hour 4), and one placebo + IEM tablet without food (approximately hour 6). The clinic staff recorded the time of each IEM ingestion, and the time that ingestion was detected by the software application on the smartphone. The primary endpoint, accuracy of IEM detection following ingestion, was 76.7% overall. The secondary endpoint, latency between IEM ingestion and time of detection by the smartphone was a mean of 1.1 minutes for placebo + IEM and a mean of 5.1 minutes for aripiprazole + IEM.

Trial 316-13-206b was a phase 4, exploratory substudy in 29 healthy male and nonpregnant female subjects 18 to 65 years of age. The primary objective was to measure the accuracy of IEM detection by the disposable Wearable Sensor Version 5 (DW5) patch following application of a single patch to the subject followed by 4 IEM ingestions. Subjects ingested one placebo + IEM tablet approximately every 2 hours (hours 0, 2, 4, and 6) for a total of 4 ingestions. Clinic staff paired and placed the patch and recorded the time of each ingestion. The smartphone was checked at 30 minute intervals for detection of the IEM and the time it was detected was recorded. The proportions of IEMs ingested

that were detected by the patch were 96.6%, 93.1%, 96.6%, and 100% at hours 0, 2, 4, and 6, respectively. The mean latency periods between ingestion of the IEM to patch detection were 1.2, 1.3, 1.1, and 1.3 minutes at hours 0, 2, 4, and 6, respectively. The mean latency periods from patch detection (acquisition time) to the time of detection in the Otsuka Cloud-based server (server time) were 7.5, 10.3, 6.2, and 6.2 minutes at hours 0, 2, 4, and 6, respectively. The range of the latency period at all scheduled time points was 0.4 to 123.2 minutes.

Trial 316-14-220 was a phase 2a, open-label trial in male and nonpregnant females 18 to 65 years of age (inclusive) with SCH who were stable on oral aripiprazole. During the trial, the subjects continued on same strength tablets consisting of aripiprazole embedded with an IEM. Subjects enroled under the original version of the protocol (using the RP4 patch with the Otsuka Medical Software component v1.4.5 and healthcare provider portal v1.4) comprised a first cohort (Cohort 1), while subjects enroled under Amendment 1 (using the DW5 patch with the Otsuka Medical Software component v1.5.2 and healthcare provider portal v1.5) comprised a second cohort (Cohort 2). Each cohort included only one treatment group; there was no control group. A total of 37 subjects were enroled and treated in Cohort 1, and a total of 30 subjects were enroled and treated in Cohort 2.

The primary objective was to measure the usability of the DMS with regard to pairing and applying the patch independently by the end of the Week 8 visit. The secondary endpoints were: the proportion of subjects who were able to pair and apply a patch successfully by the end of the Week 8 visit (or early termination [ET] if applicable) independently or with minimum assistance, and the proportion of time during the trial period when subjects wore the patches. The primary endpoint for successful pairing was defined as a score of 91 to 100 on the Subject Ability to Use System Scale–HCP version; the secondary endpoint for successful pairing was a score of 71 to 100 on the same scale.

The trial included a screening period of ≤ 2 weeks, a treatment period of 8 weeks, and a safety follow-up period of 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. For the primary endpoint, over half of the subjects overall (37 of 67, 55.2%) were able to pair and apply a patch independently and successfully by Week 8 (95% CI: 42.6%, 67.4%). Results were similar between Cohorts 1 and 2. For the secondary endpoints: 55 of 67 (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%). Overall, subjects wore their patches for a mean (standard deviation [SD]) of 70.7% (24.7%) of the trial period.

Trial 316-14-221 was an exploratory, noninterventional, open-label, 4-week trial in 37 healthy volunteers (sponsor employees), age range 28 to 63 years. The objective was to develop the functionality of the digital health data platform and confirm successful integration of appropriate data streams generated within DM source databases. Corresponding primary endpoints were the following: establishing data streams from the DM source, collecting data via live data streams, and developing an operational web-based dashboard. Results showed these endpoints were adequately achieved. Furthermore, results from this trial helped guide changes to enhance long-term performance and data collection strategies.

Trial 316-13-215 was a phase 2 multicentre, 8-week, open-label, single-arm, exploratory trial in 49 males and nonpregnant females 18 to 65 years of age (inclusive) with SCH, MDD, or BP1 who were stable on oral aripiprazole. During the trial, the subjects continued on same strength tablets consisting of aripiprazole embedded with an IEM. The objectives of this trial were to assess the functionality of an integrated call centre for the DMS and to explore the use of the DMS as measured by patch wear time, subject and HCP engagement, and subject satisfaction with the system. Results showed these endpoints were adequately achieved and for nearly all questions on the engagement and satisfaction questionnaires, the majority of subjects, physician and caregivers chose favorable responses.

The primary objective of the current trial is to explore the acceptance and performance of the DMS with HCPs and adult subjects with SCH, schizoaffective disorder, or first episode psychosis.

1.2.1 The Digital Medicine System

In this trial, the DMS consists of:

- CoEncapsulated product - an approved antipsychotic drug co-encapsulated with CE-marked MIT (CoE product);
- Patch + MDDS - an CE-marked compatible medical device; and
- Otsuka Medical Software - a local and remote computing application.

In addition, the system includes computing applications that reside both locally (eg, on a mobile computing device) and remotely (eg, on remote server, “cloud-based”) and enable

data transfer and display on the subject's mobile computing device (eg, smartphone) and on a secure web dashboard for the HCP and caregiver/support person (if applicable).

The ingestible sensor (ie, IEM) is food particle-sized and consists of minute amounts of essential minerals which occur naturally in the body and in food. It has dimensions of 1.0 × 1.0 × 0.33 mm with a core of silicon, an outer layer of cuprous chloride (CuCl) (5.3 mcg Cu extractable), and an opposing outer layer of magnesium (Mg) (5.6 mcg extractable). The ingestible sensor is contained within a placebo (Pill) that is composed entirely of excipients that are listed in Generally Recognized as Safe guidance and by the International Pharmaceutical Excipients Counsel. The major excipient (approximately 97%) is microcrystalline cellulose which is commonly used in approved medicinal tablets. The device is a CE-marked class IIa medical device (CE 559373) by the BSI.[13]

The first DMS product (Abilify MyCite®) is approved by the US FDA.

1.3 Known and Potential Risks and Benefits

1.3.1 Overview

The technology that underlies the DMS has received CE marking status in the EU and FDA clearance in the US. For safety, toxicology, and efficacy of the IEM, reference is made to Proteus Digital Health 510(k)s K113070 (DEN120011), K131009, K131524, K133263, and CE 559373. For additional information, please see the IB.[13]

To date, all of the clinical investigations of the prototype Proteus Digital Health Feedback System™ and its patch component in the US have been designated as nonsignificant risk trials because they have met the established regulatory criteria for a nonsignificant risk device trial.

Specifically, the system and the patch are not:

- An implant used to support or to sustain human life;
- Being used for substantially diagnosing, curing, mitigating or treating disease or preventing impairment of human health; or
- A potential serious risk to the health, safety, or welfare of subjects.

No serious treatment-emergent adverse events (TEAEs) and no UADEs have been reported. The vast majority of the device-related nonserious AEs that have been reported in completed trials have been classified as mild in severity.

The risk profiles of aripiprazole, olanzapine, quetiapine, and risperidone are well understood and are detailed in the approved product summary of product characteristics.[14,15,16,17]

Nonclinical studies, pharmacokinetic/pharmacodynamic trials, and other clinical trials demonstrate the efficacy and safety of aripiprazole, olanzapine, quetiapine, and risperidone.

The marketing authorisation application (MAA) for aripiprazole was approved via the centralized procedure in the EU in 2004 for the treatment of SCH in adults and in adolescents aged 15 years and older. It is indicated for the treatment of moderate to severe manic episodes in BP 1 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. It is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in BP 1 disorder in adolescents aged 13 years and older.

The MAA for risperidone was approved via the Mutual Recognition Procedure (MRP) in the EU in 1997 for the treatment SCH, moderate to severe manic episodes associated with bipolar disorders, short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

For the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with subaverage intellectual functioning or mental retardation diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment.

The MAA for olanzapine was approved via the centralized procedure in the EU in 1996 for the treatment of SCH, in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. Olanzapine is indicated for the treatment of moderate to severe manic episode. In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder.

The MAA for quetiapine was approved via the MRP in the EU in 2000 for the treatment of SCH, BP disorder (moderate to severe manic), major depressive episodes in BP disorder and for the prevention of recurrence of manic or depressed episodes in patients with BP disorder who previously responded to quetiapine treatment.

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1.3.2 Risks Related to the Digital Medicine System

1.3.2.1 Skin Findings at the Site of the Patch Attachment

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

Several mitigations will be implemented to reduce the risk of these hazards. From a materials standpoint, the patch has been designed and manufactured by a respected medical device vendor, under Good Manufacturing Practices, from components and medical-grade materials that have individually passed required biocompatibility testing. The patch adhesive meets the International Organization for Standardization 10993 standards on biocompatibility. These facts underpin a favorable biocompatibility assessment of the patch (see the IB[13] "Biocompatibility" for more details).

Skin will be monitored for irritation or changes at the site(s) of patch placement by the HCPs during HCP visits. Subjects will be trained to self-monitor their skin at the sites of patch placement between HCP visits. The patch should be replaced once per week (ie, once every 7 days) during the trial (Section 3.2.1.2). It should be noted that in early trials, the protocol-required repeated placement of the patch over the xyphoid, which may have contributed to the incidence of cutaneous AEs; in contrast, the subjects in the present trial will have latitude to rotate the patch location. Should skin changes arise, then the simplest intervention will be to move the patch to a different site on the torso. Subjects will also be told that they are free to remove the patch at any time, and that if they do they must inform trial staff immediately (see Section 3.2.1.2). Subjects whose frequency or intensity of skin changes is unacceptable can be withdrawn from the trial by the HCPs.

Finally, since the patch has an adhesive backing for long-term wear, some skin irritation may result from removing the patch because it retains a significant amount of adhesion.

To reduce this possibility, subjects will be provided adhesive remover wipes, which can be used to ease any discomfort from patch removal.

If the patch falls off, the subject should replace it with another available patch and inform the site staff.

The DMS is not expected to add any appreciable risk to the inherent risks of the trial population.

1.3.2.2 Allergic Reaction

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

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

1.3.2.3 Changes in Stool Habits

The majority of the excipient materials used in the CoE product (and internal components of the IEM formulations) are cellulose-based. Cellulose in high oral doses is commonly used as a stool softener. Stool softeners typically increase the bulk and potentially the frequency of bowel movements, but they rarely cause diarrhea. However, the quantities of cellulose-based excipients in a daily dose of a CoE product in this trial are several fold smaller than the therapeutic dose used for stool-softening purposes. No increased stool frequency was reported by subjects in previous trials, while 2 instances of constipation were reported.

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

1.3.2.4 Anxiety from the Use of the Digital Medicine System

Subjects may experience anxiety related to swallowing the CoE product, wearing the patch, or using the smartphone. Moreover, it is theoretically possible that subjects could feel uncomfortable with the concept of 24-hour data collection. To reduce potential subject anxiety, adequate training time along with clinical and technical support will be

made readily available during the trial. Moreover, familiarity with a smartphone is an inclusion criterion (see Section 3.4.2).

1.3.2.5 Potential Theoretical Digital Medicine System-related Risks

1.3.2.5.1 Procedure-related Risks

1.3.2.5.1.1 Communications-related Risks

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

To mitigate this problem, only the subjects who have the capacity to utilise the technology interfaces (eg, open and navigate software applications using the touch screen) and telephone features of a smartphone will be enroled in this trial (see Section 3.4.2).

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

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

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

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

1.3.2.5.1.2 Less Significant Procedure-related Risks

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

Additional information may be found in the IB.[13]

1.3.3 Benefits

There is a potential benefit from participating in the trial, in that subjects may have a better understanding of their medication-taking pattern and the relationship to their

illness. In addition, subjects may have a better understanding of their personal physiologic status (eg, activity, rest) by viewing the individualised health data on their smartphone.

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

1.3.4 Potential Benefits of the Digital Medicine System

1.3.4.1 Limitations of Current Medication Adherence Measures

Consequences of adherence problems in psychiatry include relapse, hospitalisation, suicide, and poor prognosis.

Physician and self-report are most commonly used to assess adherence[18] yet trials have constantly found that HCPs' subjective judgment of medication adherence are often inaccurate, with a tendency for practitioners to overestimate subject adherence. As illustrated in Figure 1.3.4.1-1, Byerly and colleagues found electronic medication cap checks detected significantly greater nonadherence rates than prescribers.[19]

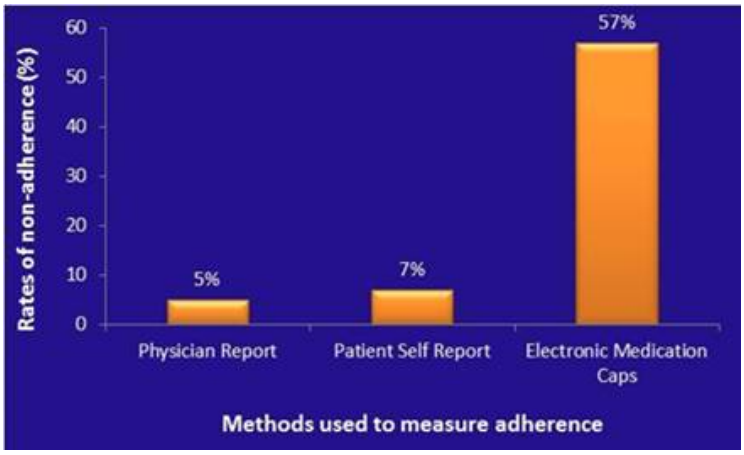

Figure 1.3.4.1-1 Methods Used to Assess Antipsychotic Medication Nonadherence for up to 6 Months

(Adapted from Byerly et al, 2007)[19]

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Drawing on a wider suite of adherence measures, one published report indicated there was an underestimation of the extent of nonadherence by subjects and physicians compared with more objective adherence measures[18,20]; methods used to measure antipsychotic medication adherence for up 12 weeks in SCH subjects are summarised in Figure 1.3.4.1-2. The tendency for physician overestimation of adherence has also been reported in bipolar disorder.[21]

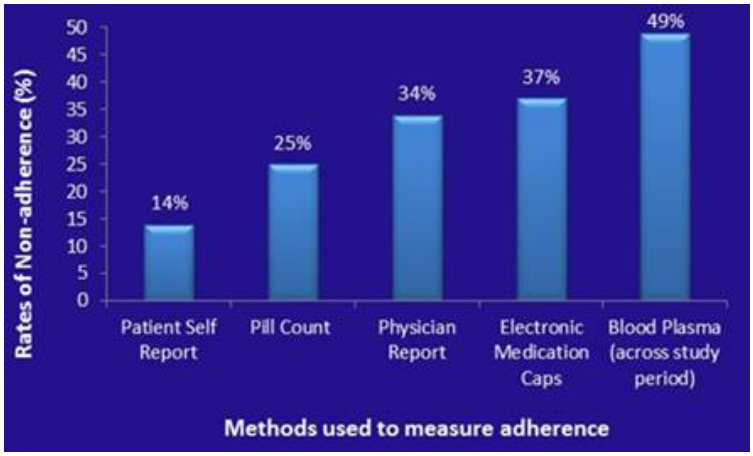

Figure 1.3.4.1-2 Methods Used to Measure Antipsychotic Medication Adherence for up to 12 Weeks

(Adapted from Velligan et al, 2007)[22]

1.3.4.2 Potential Benefits of the Digital Medicine System Adherence Measures

The DMS includes a CoE product providing an advance on the available proxy measured by the following:

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

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

2 Trial Rationale and Objectives

2.1 Trial Rationale

A number of subject behaviours are known to be either barrier to successful treatment and/or predictors of worsening of psychiatric condition. The use of devices and mobile health technologies have become available that may improve health management and subject outcome in mental health disorders. Otsuka Pharmaceutical Company Ltd. is developing a DMS to measure subject parameters to facilitate better care for mental health service users and better outcomes for the healthcare system.

The intention of the DMS is 2-fold. Firstly, it will enable subjects and HCPs to use the available data to support subjects care and engage the subjects in their ongoing disease management, encouraging greater self-management and behaviour change through access to information. Secondly, the system will allow HCPs and caregivers/support persons to use this information to improve the subjects care.

2.2 Dosing Rationale

The subjects in this pragmatic trial will receive CoE MIT and drug originator tablet of either aripiprazole, olanzapine, quetiapine, or risperidone as prescribed by their HCPs.

The treatment medication decision will be determined by the HCPs and independent from the protocol.

2.3 Trial Objectives

The primary objective of this trial is to explore the acceptance and performance of the DMS with HCPs and adult subjects with SCH, schizoaffective disorder, or first episode psychosis.

3 Trial Design

3.1 Type/Design of Trial

This is a multicentre, 8-week, single-arm, open-label, pragmatic trial to explore the acceptance and performance of using the DMS with HCPs and adult subjects with SCH, schizoaffective disorder, or first episode psychosis on an oral atypical antipsychotic (aripiprazole, olanzapine, quetiapine, or risperidone).

This trial includes a screening/baseline visit (up to 7 days), an assessment period (8 weeks), safety follow-up phone call (2 weeks after Week 8/ET visit), and the healthcare utilisation record evaluation (24 weeks before and after the baseline visit for a total of 48 weeks).

Subjects in this trial will receive an initial introduction to the DMS, and have HCP visits at screening/baseline, Week 4, Week 8/ET, and as directed by the HCP for the duration of the subject's participation in the trial.

Subjects entering the trial will be treated with one of the oral atypical antipsychotics defined in the trial. The treatment medication decision will be determined by the HCPs and independent from the protocol.

The HCPs will have access to a DM dashboard where notifications can be setup around medication ingestion.

Screening/Baseline Visit (Days -7 to -1)

After providing the informed consent, subjects will enter the screening period for up to 1 week (7 days). Screening and baseline may occur at a single visit or may occur over 2 visits up to 7 days apart. The screening period may be extended at the discretion of the HCP.

Recruitment will be facilitated by firstly using the research sites sharing information about research remote function call procedure, which records subject's preferences in relation to being directly contacted by researchers about any future research studies for which they may be eligible. Their electronic health records (EHR) reflect this 'opt in' status. The subjects who have already 'opted in' to be contacted about future research will be approached by the research team.

Secondly, Clinical Interactive Record Search (CRIS) will be utilised to interrogate de-identified patient records for those who have opted into CRIS. The trial will be submitted to the CRIS monitoring group for approval to access the CRIS application.

Assessment Period (8 weeks):

Initiation of the DMS will commence at the baseline visit, with subjects ingesting the CoE product, wearing the patch, and using the smartphone app for a total of 8 weeks during the assessment period from baseline visit to Week 8 visit.

During the assessment period from baseline visit to Week 8/ET visit:

- Subjects will visit the HCP for clinical evaluations at Week 4;
- Subjects will collect their DMS prescription refill at Week 4 visit for next 4 weeks until Week 8/ET visit;
- Subjects will visit the HCP at Week 8/ET and undergo another clinical evaluation.

Safety and tolerability data will be collected and evaluated on an ongoing basis, as assessed by the frequency and severity of serious adverse events (SAEs), and device-related nonserious AEs.

Subjects will be monitored on the technology by the HCPs, who will review the HCP dashboard data at a minimum of every 2 weeks and make changes to current treatment plan and therapy at their discretion. The HCPs may request that a subject return to the site for unscheduled visits as deemed appropriate. In the event of an unscheduled visit, review of the DMS dashboard and safety events will be collected.

Follow-up:

Week 8/ET visit evaluations will be completed for any subject withdrawn from the trial at any time (for any reason other than full withdrawal of the consent).

Following the Week 8/ET visit, the subjects will not use the DMS and return to standard care (routine follow-up from care teams and continue non-DM medications). Subjects will have access to their trial account or data in the smartphone app up until 30 days after the last subject's Week 8/ET visit. After this duration, the subjects will no longer have access to their data via the smartphone app.

A safety follow-up phone call will occur at 2 weeks after the Week 8/ET visit, which will be the last official subject contact.

Healthcare Utilisation Record Evaluation (24 weeks before and after the baseline visit):

Twenty-four weeks before and after the baseline visit (for a total of 48 weeks), all hospital admissions (psychiatric and non-psychiatric) would be recorded and assessed as either 'planned' or 'unplanned' and 'related' or 'unrelated' to the psychiatric illness. Similarly, all encounters between any HCP (psychiatric and non-psychiatric) and the subject will be recorded to obtain the following information:

- The nature of the contact (eg, home visit, inpatient, outpatient, HCP visit, day centre);
- The HCP role (eg, community psychiatric nurse);
- Whether the contact was planned or not;
- Whether or not the contact was initiated as a result of data from the DMS;
- Any medication titration, adherence counseling, education, and lifestyle coaching.

This data will be reported in the data collection tool at Week 24 (or up to 7 days after this time point).

The trial schematic is summarised in Figure 3.1-1.

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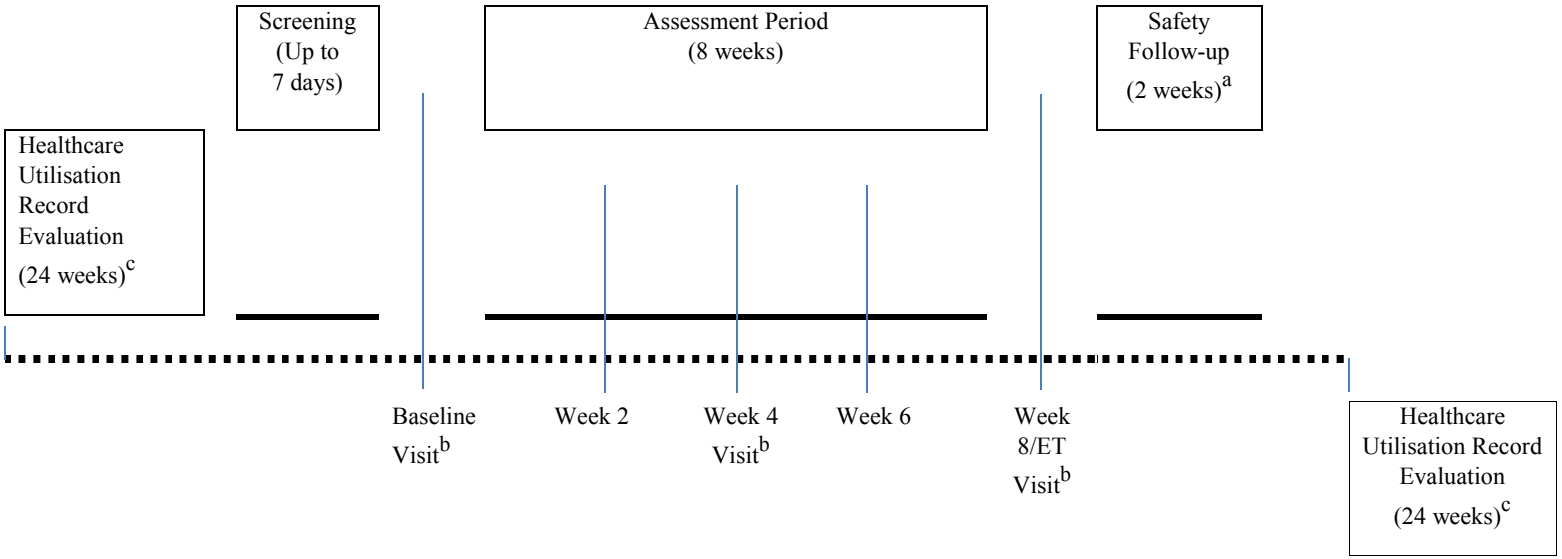

HCPs will review HCP dashboard at Weeks 2, 4, 6 and 8 and make treatment changes at their discretion.

[a]Safety follow-up phone call will occur 2 weeks after Week 8/ET visit.

[b]Subject visits will occur at baseline, Week 4 and Week 8/ET. Other visits will be at the discretion of the HCP.

[c]Healthcare utilisation will be recorded 24 weeks before and after baseline visit (for a total of 48 weeks), at Week 24.

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

The subjects will receive CoE MIT and drug originator tablet of either aripiprazole, olanzapine, quetiapine, or risperidone as prescribed by their HCPs (see Section 2.2). The originator drug tablet will be known as either DM-Aripiprazole, DM-Olanzapine, DM-Quetiapine, or DM-Risperidone within the smartphone app.

The subject and the HCP will initiate the system at the baseline and use it for 8 weeks (from baseline to the Week 8/ET visit). Following this period, the use of the DMS will be stopped and the subject will return to standard care (routine follow-up from care teams and continue non-DM medications). The DMS may be started and stopped as clinically appropriate based on HCP's judgment during the 8-week assessment period of the trial.

Following the Week 8/ET visit, the subjects will not use the DMS and return to standard care (routine follow-up from care teams and continue non-DM medications). Subjects will have access to their trial account or data in the smartphone app up until 30 days after the last subject's Week 8/ET visit. After this duration, the subjects will no longer have access to their data.

3.2.1 Digital Medicine System Components and Use

The DMS includes a drug-device combination of a CoE product, a patch, and an application software to convey level of activity and rest, and to mark events through the act of ingestion.

The CoE product is the drug-device combination which consists of an antipsychotic medication and MIT. The active drug-device combination in this trial will be the drug originator tablet of either aripiprazole, olanzapine, quetiapine, or risperidone + IEM.

The patch is a separate compatible medical device, which consists of a Wearable Sensor and an associated compatible medical device software application from Proteus Digital Health Inc. The patch is an unmedicated adhesive device that is worn within a specified torso area on the left side (Section 3.2.1.1). Each patch is designed for 7-day wear; extra patches will be provided should the subject be required to change the patch more frequently (ie, patch falls off prematurely or patch becomes partially adherent to skin). The patch detects and time-stamps each IEM ingestion as well as measures and records other date- and time-stamped physiologic and behavioural data, such as heart rate, physical activity (ie, step count), and amount of rest. The patch connects wirelessly to a commercially available mobile computing device (ie, smartphone) to transfer data

captured by the patch via the compatible medical device software application to a secure server for aggregation and processing.

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

Subjects should own a commercially available smartphone or a smartphone will be provided by the Sponsor, and be familiar with its use (ie, iPhone 7s and 10.x, android Samsung s8 and Os 7.x). The smartphone should be charged daily (however, it is noted that if the smartphone battery becomes fully depleted, the DMS data will not be lost, as the data will remain stored on the patch). Subjects will be requested to carry the smartphone with them as much as possible, and to plug in the device at a dedicated location at home where they have easy and frequent access when not being carried. The preferred location is on a bedside table or location immediately adjacent to where the subject sleeps.

The subject may view his/her data at will on the smartphone. In addition, the subject's selected HCPs and selected caregivers/support person (if applicable) can view this information via the cloud-based server. HCPs can set up missed dose notifications to monitor any lapses in subject's adherence. HCPs will review for HCP dashboard at Weeks 2, 4, 6 and 8 at minimum and make treatment changes at their discretion.

Each HCP will be provided with a printed DMS reference guide that will provide explicit directions for normal use and troubleshooting.

At each visit, subjects will be reminded by the HCP to contact the integrated call centre with any technical questions about the DMS. The call centre will operate from Monday to Friday from 9 AM to 5 PM (Greenwich Mean Time).

If there are any technical issues with the DMS that the integrated call centre is unable to resolve, the subject will be routed to a technology support representative. If a subject contacts the integrated call centre with clinical issues including reporting of SAEs, the integrated call centre will document the event and forward the information to the trial site for additional follow-up, as needed.

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3.2.1.1 Digital Medicine System Onboarding

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

The patch is to be placed on the left side of the torso within a defined zone just above the lower edge of the rib cage.

The defined zone on the torso must meet all of the following parameters:

- On the left side;
- Just above the left costal margin;
- From the xyphoid process to the left mid-axillary line;

Placement should be on the lower chest with the lower edge of the patch on the lower edge of the rib cage, and NOT on the abdomen.

Patch placement location is depicted visually in Figure 3.2.1.1-1.

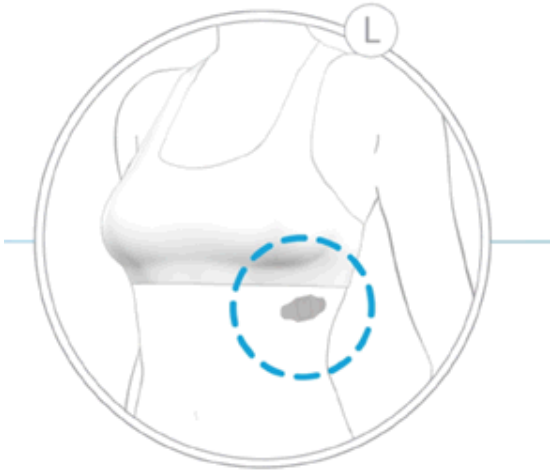

Figure 3.2.1.1-1 Patch Placement Zone

A simple skin preparation procedure, consisting of gently cleaning the skin surface with an alcohol wipe and allowing the area to dry, is recommended. On some subjects, clipping of body hair in the placement zone may be required to allow secure device adhesion. Placement of the patch should avoid locations below the bottom of the rib cage or areas where the patch was previously worn. Use of lotions on the skin where the patch will be place is not recommended. The patch can be worn during regular activities,

including showering, but new patches should not be applied for a few hours after showering or other physical activities to ensure the adhesive sticks properly. Patches can be worn up to 7 days, at which point, the smartphone app will remind patients that the patch needs to be changed.

During the DMS onboarding process, the smartphone app will provide a message to prompt the subject to ingest a CoE product to verify and confirm the proper setup of the DMS.

A patch may be placed anywhere in the zone depicted in Figure 3.2.1.1-1; however, when an old patch is replaced with a new patch, each new patch must be placed on a **different skin location (with no overlap)** from where the last one was just removed.

Upon completion of each patch application, before a new patch can be paired and applied, the wireless connection between the Wearable Sensor and the smartphone app must be confirmed so that all data have been transferred appropriately (see Section 3.2.1.2).

3.2.1.2 Digital Medicine System Patch Use

Once every 7 days throughout the assessment period, the subject will pair a new patch with the application and then apply it to his or her torso in the proper location. Each patch should be removed on the seventh day after the day of the initial application of that patch; no patch should remain applied to a subject's skin for longer than 7 days.

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

A subject will be told that it is allowable to remove the patch for any reason (especially for evidence of local skin irritation/inflammation), but that it is preferred that the patch be kept on as much as is tolerable and safe. The subject should note, as much as possible, the events surrounding any premature removal of the patch and contact the site immediately.

Although a given patch generally should indeed be applied for a full 7 days, in some cases a patch might end up being replaced before the 7 days is up (eg, if a previous patch falls off prematurely or if a subject removes a patch because of local skin irritation/inflammation). Instances of patch removal (unintentional or intentional) less than 7 days after the patch has been applied will constitute premature patch removal.

A reason must be recorded for every patch removal, including reasons for premature patch removal.

Each time a previous ("old") patch is removed (or inadvertently falls off), a new patch should be paired and applied immediately.

Subjects are free to replace a patch offsite using dispensed trial supplies. A subject will then pair the new patch with the smartphone, prepare the skin for placement of the patch, remove the backings of the new patch to expose the adhesive layer, and then attach the patch to the skin at the proper position on the torso.

Each subject will return all supplies, including all used patches and associated labels, to the trial site. At the end of the trial (Week 8/ET visit), all returned patches and associated labels will be destroyed at the trial site(s) or by a designated agent.

3.2.1.3 Digital Medicine System Versions

Different versions of the DMS have been developed.

The version of the DMS that will be evaluated is the Archer IEM and DW5 patch combination (Archer/DW5) with Digital Medicine software application Version 2.1 (iOS and Android).

3.3 Trial Population

Adult subjects with SCH, or schizoaffective disorder, or first episode psychosis, who are prescribed either aripiprazole, olanzapine, quetiapine, or risperidone and meet eligibility criteria will be enroled in this trial.

3.3.1 Number of Subjects and Description of Population

The trial will enrol approximately 60 male and female adult subjects between 18 and 65 years of age, inclusive, with a confirmed clinical diagnosis of SCH or schizoaffective disorder (defined by International Classification of Disease [ICD]-10 codes F20 and F25), or first episode psychosis using case note review. There is no limit on the duration of illness for those with SCH or schizoaffective disorder but first episode psychosis is defined as less than 3 years since presentation to the mental health team or first antipsychotic prescription. Subjects will receive care under at least one of the following care settings:

- Discharge from a hospital admission (within 7 days) to an acute intervention team;
- Referral to an acute intervention team, prior to any hospital admission;
- Referral from an acute intervention team to a community mental health team;

- Managed by community services (inclusive of patients on Care Programme Approach);
- Inclusion within early intervention caseload (< 3 years from initial symptoms);
- HCP determines the subject would benefit from using the DMS.

3.3.2 Subject Selection and Numbering

All subjects will be given a unique 5-digit subject ID number.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). Consent will be documented on a written informed consent form (ICF). Caregivers/support persons (if applicable) will also be required to sign an ICF. The ICF will be approved by the same independent ethics committee (IEC) that approves this protocol. Additionally, the informed consent will cover the retrospective and prospective aspects of the trial.

Each ICF will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[23] and local regulatory requirements. The HCP will ensure that the sponsor reviews and authorises any written site-specific ICF used in the trial before submission to the IEC.

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

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

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the HCP (or designee), and it has been documented that the subject has had the opportunity to ask questions, the IEC-approved written ICF will be signed and dated by both the subject and the person obtaining consent (HCP or designee), as well as by any other parties required by the IEC. The subject will receive a copy of the signed ICF; the original shall be kept on file by the HCP.

Subjects may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria

1.	Subject must be willing and able to give written (signed and dated) informed consent, which includes adherence to trial requirements and restrictions before enroling in the trial. Subject must be willing to adhere to trial procedures, including troubleshooting of the DMS by a third party if needed.
2.	Subject must be able to read and understand English.
3.	Male and female subjects 18 to 65 years of age, inclusive, at the time of informed consent.
4.	Subject possessing their own smartphone or a smartphone provided by the Sponsor, and being familiar with its use and willing to download and interact with the DMS app, completing all tasks as well as adequately operate all devices, as applicable. Caregiver/support person or other third party assistance can be utilised, if needed, although all subjects should be encouraged to attempt all tasks themselves.
5.	Subject possesses the capacity to utilise the technology interfaces (eg, open and navigate software applications using the touch screen) and telephone features of a smartphone. The subject has satisfactory mobile phone reception (preferably 3 bars or more, or have Wi-Fi) at home and/or at work for trial-designated wireless carrier.
6.	Subject is cooperative, able to ingest oral medication, willing to complete all aspects of trial, and capable of reporting AEs.
7.	Clinical diagnosis of SCH or schizoaffective disorder (defined by ICD-10 codes F20 and F25) or first episode psychosis using case note review.
8.	Subjects prescribed aripiprazole, olanzapine, quetiapine, or risperidone.
9.	Subject must fulfill at least one or more of the following: • Discharge from a hospital admission (within 7 days of discharge) to an acute intervention team; • Referral to an acute intervention team, prior to any hospital admission; • Referral from an acute intervention team to a community team; • Managed by community services (inclusive of patients on Care Programme Approach); • Inclusion within early intervention caseload (< 3 years from initial symptoms); • HCP determines the subject would benefit from using the DMS.
10.	Subject's general medical condition such that participation in the trial does not pose any additional risk as per HCP's judgment.
11.	Skin on the anterior chest just above the lower edge of the rib cage that is free of any dermatological problems (eg, dermatosis or dermatitis, open wounds, or other skin disorders such as warts, rashes, atopic dermatitis, or irritations).

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3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria

1.	Subject with any disorder including but not limited to intellectual developmental delay or disorder, major neurocognitive disorder or other condition that may impact the subject's ability to participate in the trial or interact with the smartphone application.
2.	Subject who is likely to be incapable of using the DMS technology, even with assistance.
3.	Subject who has a history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere with assessments of safety or usability during the course of the trial, including but not limited to, hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the HCP.
4.	Subject with a known allergy to adhesive tape or any pertinent components of the patch or CoE product.
5.	Prisoner must not be enroled into this trial.
6.	Subject who is hospitalised due to mental or physical illness (inpatient) at the time of screening/baseline must not be enroled into this trial.
7.	Any subject who, in the opinion of the HCP, should not participate in the trial.
8.	Any subject who, through religious or lifestyle choices, will not take gelatin capsules.
9.	Female (FOCBP) who is breast-feeding and/or who have a positive pregnancy test result prior to receiving trial enrolment, or who plans to become pregnant during the trial.

FOCBP = females of childbearing potential.

Individuals that are sectioned as part of the Mental Health Act (MHA), yet remain in the community (eg, community treatment orders) will be able to participate in the trial providing all inclusion criteria are met. However, individuals that are sectioned as part of the MHA and are compulsory detained in a hospital or secure setting (eg, inpatient) will not be able to participate in the trial.

Individuals will be able to take two or more of the 4 DMs in the study, should the HCP deem it necessary (eg, DM-Aripriprazole and DM-Quetiapine).

Individuals may be switched from their current medication to one of the 4 DMs prior to enrolment only if considered medically appropriate. No subject should be switched to one of the 4 DMs for the purpose of meeting trial entry criteria.

In respect to other examples of polypharmacy (eg, typical antipsychotics, atypical antipsychotics, mood stabilisers, antidepressants, or indeed other medication), individuals will be able to participate providing they are prescribed one of the four antipsychotics under investigation (eg, aripiprazole, olanzapine, quetiapine, or risperidone).

Subjects will be able to participate if they are taking a long-acting injectable/depot, providing that mediation is not the same as the oral equivalent in this trial:

- Allowed (eg, flupentixol [Depixol®, Fluanxol®, flupenthixol] depot and DM);
- Not allowed (eg, Risperdal Consta® and DM-Risperidone, Abilify Maintena® and DM-Aripiprazole).

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

Subjects must agree to restrictions to medications and lifestyle as described in Section 4.

3.5 Endpoints

3.5.1 Primary Endpoint

The primary endpoint is the proportion of days with good patch coverage during the trial, which is calculated by the number of days with good patch coverage divided by the total number of trial days for each subject. The good patch coverage will be defined as having at least 80% patch data available or MITs detected within the 24-hour period for each day while the subject is on the trial.

3.5.2 Secondary Endpoint

The secondary endpoint is subject's adherence metric, which is the proportion of detected MITs over the expected MITs ingested during the trial days with good patch coverage.

3.5.3 Exploratory Endpoints

The exploratory endpoints are as follows:

1) To explore the acceptance and performance of the DMS with HCPs and adult subjects with SCH, schizoaffective disorder, or first episode psychosis as measured by:
   - The proportion of time during the trial period when the subject wears their patch.
   - The engagement and satisfaction of subjects, HCPs, and caregivers/support persons (if applicable), as determined by the surveys (Subject Usability and Satisfaction Scale, HCP Utility Survey, and Caregiver/Support Person Involvement Scale [if applicable]).

- The proportion of days subjects are using the application and the proportion of days that HCP are using the HCP dashboard during the trial.
- The proportion of ingested MITs registered on the digital health data server versus expected MITs ingested.

2) Additional variables will be captured to better understand outcomes that may impact use of the DMS or be impacted by the use of the DMS including:
   - Change from baseline to Week 8/ET in Clinical Global Impression-Severity of Illness Scale (CGI-S);
   - HCP visits and associated setting of care;
   - Details surrounding any hospitalisations;
   - Occurrence and timing of community/home visits;
   - Any referrals during the observation period.

3.5.4 Safety Variables

The safety variables are as follows:

- Evaluate the safety and tolerability of the DMS, as assessed by the frequency and severity of SAEs, and device-related nonserious AEs;
- Evaluate suicidality;
- Evaluate any product quality complaints that arise.

3.6 Measures to Minimize/Avoid Bias

This trial is open-label.

3.7 Trial Procedures

Eligible subjects will enter the screening period for up to 1 week (7 days). Screening and baseline may occur at a single visit or may occur over 2 visits up to 7 days apart. The screening period may be extended at the discretion of the HCP. At the screening/baseline visit, informed consent will be obtained before any trial-related assessments or procedures are performed. Initiation of the DMS will commence at the baseline visit for the subjects who meet all applicable eligibility criteria (Section 3.4), based on a series of assessments conducted at the screening/baseline visit.

During screening/baseline visit, the HCP will provide training on the correct use and required procedures associated with the DMS. The subject will be provided with patches, CoE product, other supplies, and instructions on the procedures to be followed over the coming weeks.

Subjects will be monitored on the technology by the HCPs, who will review the HCP dashboard data at a minimum of every 2 weeks and make changes to current treatment plan and therapy at their discretion. The HCPs may request that a subject return to the site for unscheduled visits as deemed appropriate. In the event of an unscheduled visit, review of the DMS dashboard and safety events will be collected.

Subjects will visit the HCP for clinical evaluations at Week 4. During this visit, subjects will be dispensed patches, CoE product, and other supplies to last until the Week 8/ET visit.

At the Week 8/ET visit, designated assessments and procedures will be conducted.

The Week 8/ET visit marks the end of the assessment period. The subject will stop taking CoE product and will restart his/her standard care (routine follow-up from care teams and continue non-DM medications). All trial materials will be returned to the trial site. Week 8 assessments will be conducted.

A follow-up telephone contact will be made 2 weeks (± 3 days) after the last dose of CoE product (for subjects who withdraw early and for those who complete the trial).

Furthermore, 24 weeks before and after the baseline visit (for a total of 48 weeks), all hospital admissions (psychiatric and non-psychiatric) would be recorded and assessed as either ‘planned’ or ‘unplanned’ and ‘related’ or ‘unrelated’ to the psychiatric illness. Similarly, all encounters between any HCP (psychiatric and non-psychiatric) and the subject will be recorded to obtain the following information:

- The nature of the contact (eg, home visit, inpatient, outpatient, HCP visit, day centre);
- The HCP role (eg, community psychiatric nurse);
- Whether the contact was planned or not;
- Whether or not the contact was initiated as a result of data from the DMS;
- Any medication titration, adherence counseling, education, and lifestyle coaching.

This data will be reported in the data collection tool at Week 24 (or up to 7 days after this time point).

Trial assessment time points are summarised in Table 3.7-1.

Table 3.7-1 Schedule of Assessments

Assessment	Screening/Baseline[a]	Assessment Period				Follow-up	Post-treatment
	Days - 7 to - 1	Week 2[b] (± 3 days)	Week 4 (± 3 days)	Week 6[b] (± 3 days)	Week 8/ET (± 3 days)	Week 10 (± 3 days)	Week 24 (+ 7 days)
Trial site visit	X		X		X		
Safety follow-up phone contact						X	
Informed consent	X						
Inclusion and exclusion criteria assessment	X						
Smartphone (with means to communicate data [eg, suitable data plan or wireless local area networking (Wi-Fi)] connectivity options) verification	X						
Demographic information	X						
Medical/psychiatric history	X						
Urine pregnancy test for FOCBP	X						
Training on DMS[c]	X						
Suicidality assessment (face-to-face suicide risk assessment per trial site's SOPs)[d]	X		X		X		
Review of DMS dashboard data[e]		X	X	X	X		
Subject pairs and applies patch at trial site	X						
Subject Usability and Satisfaction Scale					X		
HCP Utility Survey					X		
Caregiver/Support Person Involvement Scale (if applicable)					X		
PAM-MH	X				X		
CGI-S	X				X		
PSP	X						
Dispense drug originator tablet + CoE MIT, supplies, patches	X		X				
Accountability for patches, and drug originator tablet + CoE MIT			X		X		

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Table 3.7-1 Schedule of Assessments

Assessment	Screening/Baseline[a]	Assessment Period				Follow-up	Post-treatment
	Days - 7 to - 1	Week 2[b] (± 3 days)	Week 4 (± 3 days)	Week 6[b] (± 3 days)	Week 8/ET (± 3 days)	Week 10 (± 3 days)	Week 24 (+ 7 days)
Concomitant medication	X		X		X		
Healthcare Utilisation Record Evaluation[f]							X

PAM-MH = Patient Activation Measure-mental Health; PSP = Personal and Social Performance Scale; SOPs = standard operating procedures.

[a]Screening/Baseline/Start may occur at a single visit or may occur over 2 visits up to 7 days apart.

[b]Not applicable to the subject. HCP must review dashboard only.

[c]Refresher training on DMS will be given to the subject as required per judgment of the HCP.

[d]Number of times will be determined by number of face-to-face visits at the HCPs discretion.

[e]Dashboard data is reviewed and entered into the case report form every 2 weeks during the trial (4 in total) by the HCP whether or not the HCP has personally seen the subject.

[f]Record in data collection tool all intervention data, including medical hospitalisations, psychiatric hospitalisations, accident and emergency (A and E) visits, and the number of crisis medications, from 24 weeks prior to baseline visit through Week 24 (total of 48 weeks).

3.7.1 Schedule of Assessments

3.7.1.1 Screening/Baseline Visit

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

At the screening/baseline visit, the following will be performed:

- Informed consent;
  - The subject must provide documented informed consent before any other trial assessments or procedures are performed;
  - If the subject has a caregiver/support person, that caregiver/support person also must provide written informed consent.
- Eligibility Assessment (Section 3.4);
  - All protocol inclusion and exclusion criteria will be reviewed by the HCP; only subjects who meet all of the inclusion criteria and none of exclusion criteria may be considered for further participation in the trial;
  - Smartphone verification: Each subject will be asked to confirm the availability of a suitable smartphone for the trial, in addition to confirming a suitable data plan or wireless local area networking (Wi-Fi) connectivity option is available to them. Smartphones and associated data plans provided to subjects by the Sponsor will be suitable for the trial.
- Interview the caregiver/support person (if applicable) to obtain demographic information;
- Obtain demographic information and medical/psychiatric history from EHR and/or subject;
- Obtain urine sample for pregnancy test (females of childbearing potential [FOCBP]);
- Administer the suicidality assessment (face-to-face suicide risk assessment per trial site's standard operating procedures [SOPs]);
- Subject receives training on the DMS;
- Subject attempts to pair and apply a patch;
- Complete the Patient Activation Measure-Mental Health (PAM-MH) (Section 3.7.2.2);
- Complete the CGI-S (Section 3.7.2.3);
- Administer the Personal and Social Performance Scale (PSP) (Section 3.7.3.4.1);
- Concomitant medications review;

- The following will be dispensed to the subject:
  - CoE products (drug originator tablet + MIT), supplies, and patches (prescribed dose is recorded) sufficient for 4 weeks (from Week 1 to Week 4). Containers (eg, baggies) will be included for the subject to collect and return used patches;
  - Instructions on how to install the DMS smartphone application;
  - User Guide for the DMS including introductory video and reference guides;
  - Contact information for the integrated call centre.

3.7.1.2 Assessment Period

The assessment period is 8 weeks from baseline visit to Week 8/ET visit. Subjects will have their final assessment period visit at Week 8/ET.

In the event a scheduled assessment period visit is missed by a subject, the trial site will contact the subject immediately and reschedule another visit as close to the original visit schedule date as possible. After at least 2 phone calls are attempted, a certified letter will be sent to the subject. If a rescheduled visit falls outside of the allowable time window, then the HCP must be contacted for approval to continue the subject in the trial.

3.7.1.2.1 Week 1 Through Week 4 (Between HCP Visits)

After completion of the screening/baseline visit assessments and procedures, the subject will return home until the next visit (the Week 4 visit), which will be scheduled for approximately 4 weeks later.

During this time interval, the following will occur:

- Subject wears a patch continuously;
- Subject takes CoE product (drug originator tablet + MIT) daily;
- The subject (and/or caregiver/support person, if applicable) may call the integrated call centre, if needed, for support regarding use of the DMS and its components (eg, CoE product [drug originator tablet + MIT], patch, or smartphone application).

3.7.1.2.1.1 Week 2

Week 2 (± 3 days) will not be a planned HCP visit for the subject; however, DMS dashboard data will be reviewed.

3.7.1.2.1.2 Week 4

Week 4 (± 3 days) will be a HCP visit for the subject. At the Week 4 visit, the following will be performed:

- Subject returns used and unused patches;
- Accountability of patches and CoE product (drug originator tablet + MIT) supplies performed;
- Dispense CoE product (drug originator tablet + MIT), supplies, and patches (prescribed dose is recorded) for next 4 weeks until Week 8/ET visit. Containers (eg, baggies) will be included for the subject to collect and return used patches;
- Review subject and HCP dashboards with the subject;
- Remedial training provided, if needed;
- Administer the suicidality assessment (face-to-face suicide risk assessment per trial site's SOPs);
- Monitor device-related nonserious AEs;
- Review concomitant medications.

3.7.1.2.2 Week 5 Through Week 8 (Between HCP Visits)

After completion of Week 4 visit to trial site, the subject will return home until the next visit (the Week 8/ET visit), which will be scheduled for approximately 4 weeks later (8 weeks after baseline visit).

During this time interval, the following will occur:

- Subject wears a patch continuously;
- Subject takes CoE product (drug originator tablet + MIT) daily;
- The subject (and/or caregiver/support person, if applicable) may call the integrated call centre, if needed, for support regarding use of the DMS and its components (eg, CoE product [drug originator tablet + MIT], patch, or smartphone application).

3.7.1.2.2.1 Week 6

Week 6 (± 3 days) will not be a planned HCP visit for the subject; however, DMS dashboard data will be reviewed.

3.7.1.2.2.2 Week 8/Early Termination Visit

Week 8/ET (± 3 days) will be a HCP visit for the subject. In addition, Week 8/ET visit evaluations are to be completed for any subject withdrawn from the trial at any time (for any reason other than full withdrawal of the consent). At the Week 8/ET visit, the following will be performed:

- Subject returns used and unused patches;
- Accountability of patches and CoE product (drug originator tablet + MIT) supplies performed;
- Review subject and HCP dashboards with the subject;
- Administer the suicidality assessment (face-to-face suicide risk assessment per trial site's SOPs);
- Administer the Subject Usability and Satisfaction Scale (Appendix 4);
- Complete HCP Utility Survey (Appendix 5);
- Administer the Caregiver/Support Person Involvement Scale (if applicable) (Appendix 6);
- Complete PAM-MH (Section 3.7.2.2);
- Complete the CGI-S (Section 3.7.2.3);
- Monitor device-related nonserious AEs;
- Review concomitant medications;
- Stop application of patches. Remove the final patch at the end of the visit (before the subject leaves the trial site) and retain it at the trial site;
- Restart subject's standard care (routine follow-up from care teams and continue non-DM medications). Subjects will not have access to their trial account or data in the smartphone app 30 days after the last subject's Week 8/ET visit;
- Instruct subject that they will be receiving a telephone call 2 weeks (± 3 days) later for a safety follow-up.

3.7.1.3 Safety and Safety Follow-up

A safety follow-up phone call will occur at 2 weeks (± 3 days) after the Week 8/ET visit, which will be the last official subject contact. At this time, the HCP will review SAEs and device-related nonserious AEs.

3.7.1.4 Healthcare Utilisation Record Evaluation

Healthcare utilisation record evaluation will take place 24 weeks (+ 7 days) prior to and following the baseline visit (for a total of 48 weeks) to evaluate the subject health records and to examine subject interaction with the HCPs following the DMS usage.

Twenty-four weeks before and after the baseline visit (for a total of 48 weeks), all hospital admissions (psychiatric and non-psychiatric) would be recorded and assessed as either 'planned' or 'unplanned' and 'related' or 'unrelated' to the psychiatric illness. Similarly, all encounters between any HCP (psychiatric and non-psychiatric) and the subject will be recorded to obtain the following information:

- The nature of the contact (eg, home visit);
- The HCP role (eg, community psychiatric nurse);
- Whether the contact was planned or not;
- Whether or not the contact was initiated as a result of data from the DMS;
- Any medication titration, adherence counseling, education, and lifestyle coaching.

Intervention data includes medical hospitalisations, psychiatric hospitalisations, A and E visits, outpatient visits, and the number of crisis interventions. This data will be recorded in the data collection tool at Week 24 or up to 7 days after this time point.

3.7.2 Outcome Assessments

This trial is designed primarily to explore the acceptance and performance of the DMS with HCPs and adult subjects with SCH, schizoaffective disorder, or first episode psychosis, who are on an oral atypical antipsychotic (aripiprazole, olanzapine, quetiapine, or risperidone).

The ability of subjects to interact with the DMS will be recorded in addition to recording the usability from different HCPs and caregivers/support persons (if applicable) since these make up the endpoint assessments.

Please refer to Section 3.5.

3.7.2.1 Scales to Evaluate Usability of the Digital Medicine System

- Subject Usability and Satisfaction Scale (Appendix 4);
- HCP Utility Survey (Appendix 5);
- Caregiver/Support Person Involvement Scale (if applicable) (Appendix 6).

3.7.2.2 Patient Activation Measure-Mental Health Scale

The PAM-MH is a reliable and valid measure of subject activation among individuals with serious mental health problems.[24] Subjects' feeling of their mental health will be

rated using a series of questions at screening/baseline and Week 8/ET visit. The response choices include the following:

- 1 = Strongly Disagree
- 2 = Disagree
- 3 = Agree
- 4 = Strongly Agree

A sample of the PAM-MH is provided in Appendix 7.

3.7.2.3 Clinical Global Impression-Severity of Illness Scale

The severity of illness for each subject will be rated using the CGI-S at screening/baseline and Week 8/ET visit.[25] To perform this assessment, the rater or HCP will provide a response to the question "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" Response choices include the following:

- 0 = not assessed
- 1 = normal, not at all ill
- 2 = borderline mentally ill
- 3 = mildly ill
- 4 = moderately ill
- 5 = markedly ill
- 6 = severely ill
- 7 = among the most extremely ill subjects

A sample of the CGI-S is provided in Appendix 8.

3.7.3 Safety Assessments

Assessments for safety include SAEs, device-related nonserious AEs, pregnancy tests (FOCBP only), and the suicidality assessment (face-to-face suicide risk assessment per trial site's SOPs).

3.7.3.1 Serious Adverse Events, Device-related Adverse Events, and Unanticipated Adverse Device Events

Refer to Section 5, Reporting of Serious Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

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

3.7.3.3 Suicidality Assessment

Face-to-face suicide risk assessment will be conducted per trial site's SOPs at screening/baseline, Week 4 and Week 8/ET visits, and at the discretion of HCP at any time during the trial.

3.7.3.4 Other Assessments

3.7.3.4.1 Personal and Social Performance Scale

The PSP will be administered by a rater and measures the ability of the subject to perform socially useful activities, self-care, and engage in relationships. This scale will be measured at screening/baseline only. The scale also measures whether any disturbing or aggressive behaviours are present. A global score of general functioning is also obtained using this scale. A sample of the PSP is provided in Appendix 9.

3.7.4 End of Trial

The end of trial date is defined as the last date of contact or the date of final contact attempt for the last subject completing or withdrawing from the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial

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

3.8.2 Individual Trial Site

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

3.8.3 Individual Subjects

3.8.3.1 Discontinuation of Digital Medicine System

After enrolment, a subject may stop the DMS permanently for a variety of reasons. The DMS discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to SAEs, and/or device-related nonserious AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the HCP. However, each HCP must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.4.

If any subject discontinues the trial early (including subjects who are discontinued at the Week 4 visit), every effort should be made to complete the Week 8/ET evaluations (see Table 3.7-1) at that visit. All subjects (completers and early withdrawals) will be contacted to monitor for safety events via telephone or HCP visit at 2 weeks (± 3 days) after the Week 8/ET visit.

3.8.3.2 Documenting Reasons for Treatment Discontinuation

A subject may discontinue the DMS for a number of reasons including those listed below:

- Reasons related to SAE:
  - Subject decides to discontinue because of annoyance or discomfort due to a non-serious AE which is not otherwise determined to be an undue hazard.
  - Continuing DMS places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to DMS).
    - SAEs.
    - Other potentially DMS-related safety concerns or AEs.
- Death;
- Reasons unrelated to medical condition (provide detail and review AE history with subject);
- Withdrawal of informed consent (complete written withdrawal of consent form);
- Lost to follow-up;
- Pregnancy (see Section 5.5);
- Termination of all or part of the trial by the sponsor.

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

3.8.3.3 Withdrawal of Consent

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

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

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

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt or discontinue the DMS administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1and Section 3.8.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the HCP should follow the procedures outlined in Section 3.8.3.3 to determine

if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending the DMS discontinuation or consent withdrawal, HCP will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on the use of the DMS. The HCP should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not started on the DMS.

Female subjects excluded for a positive urine pregnancy test (FOCBP) at screening are not eligible to be rescreened for participation in the trial. However, subjects excluded for any other reasons during the screening period may be rescreened at a later date. In the event that the subject is rescreened, a new ICF must be signed and a new screening number assigned.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for the objectives of the trial irrespective of whether or not the subject actually administered all relevant supplies of the DMS. Subjects who are evaluated at the last scheduled visit during the assessment period will be defined as trial completers. For purposes of this trial, subjects who complete the Week 8/ET visit will be defined as trial completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Week 8 visit during the assessment period and who do not have a known reason for discontinuation (eg, withdrew consent or SAE) will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (eg, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (eg, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status. As such, subjects will have access to their trial account or data in the smartphone app up until 30 days after recording the lost to follow-up status. After this duration, the subjects will no longer have access to their data via the smartphone app.

3.12 Subject Compliance

Subjects will be considered noncompliant if they lack adherence to the visit schedule or inappropriate or lack of the DMS use.

3.13 Protocol Deviations

This trial is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, use of improved medical device, subject enroled in violation of eligibility criteria or concomitant medication criteria), the HCP or designee will contact the sponsor's designees at the earliest possible time by telephone or e-mail. The HCP and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the HCP and the sponsor.

4 Restrictions

4.1 Prohibited Medications

Prohibited medications will be considered per approved label for each of the approved medication used in the trial.

4.2 Other Restrictions

4.2.1 Restricted Therapies and Precautions

Not applicable.

4.2.2 Non-therapy Precautions and Restrictions

4.2.2.1 Precautions

Subjects should not undergo any elective medical procedure without prior consultation with the HCP. An elective procedure (minor surgery, dental surgery, orthopedic surgery, etc.) that might require hospitalisation or anaesthesia should be deferred until after the trial, whenever clinically appropriate.

4.2.2.2 Restrictions

Subjects will be encouraged to limit the drinking of alcoholic beverages and refrain from using illicit drugs during participation in this trial.

5 Reporting of Adverse Events

In this phase 4 trial, all SAEs (ie, drug-related SAEs and device-related SAEs), device-related nonserious AEs, potential hepatotoxicity cases and pregnancies will be monitored and collected.

5.1 Definitions

5.1.1 Drug-related Serious Adverse Events

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

- Death
- Life-threatening; eg, the subject was, in the opinion of the HCP, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalisation or prolongs hospitalisation.
  - Hospitalisation itself should not be reported as an SAE; whenever possible the reason for the hospitalisation should be reported.
  - Hospitalisations or prolonged hospitalisations for social admissions (eg, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.

- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse.

5.1.2 Device-related Serious Adverse Events

A device-related serious adverse event is defined as:

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

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

If an AE is related to the patch, then the Skin Irritation Scoring System (Appendix 10) will be completed by the HCP. A photo of the affected area should also be taken using the trial provided data collection tool, if possible. Patch-related AEs grade 2 or above will be considered medically significant for purposes of this trial.

5.1.3 Device-related Nonserious Adverse Events

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

5.1.4 Nonserious Adverse Events

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE (Section 5.1.1 and Section 5.1.2) and device-related nonserious adverse events (Section 5.1.3).

5.1.5 Immediately Reportable Event

Immediately reportable events (IREs) include the events discussed in Section 5.1.1, Section 5.1.2, and any of the following outcomes:

- Any SAEs;
- Any device-related nonserious AEs related to occupational exposure;
- Potential drug-induced liver injury (DILI) case (see Section 5.4);
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate DMS discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented as an AE in the data collection tool, if there is an abnormality or complication.

5.1.6 Abnormal Clinical Laboratory Test Changes

Clinical laboratory assessments will be conducted at the HCPs' discretion to ensure safety of the subject. However, aside from the urine pregnancy test at screening, ongoing clinical laboratory assessments are not required for this trial. In the event that the HCP orders a laboratory test in the interest of subject safety, it is the HCP's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the HCP's dated signature on the laboratory report. For each abnormal laboratory test result, the HCP needs to ascertain if this is abnormal (eg, clinically significant) for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The HCP may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the HCP (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory

value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

5.1.7 Severity

Adverse events will be graded on a 3-point scale and reported as indicated in the data collection tool. The intensity of an adverse experience is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

5.1.8 Digital Medicine System Causality

Assessment of causal relationship of an SAE or device-related nonserious AE to the use of the CoE product, patch, or smartphone is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the DMS and the SAE or device-related nonserious AE.

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

5.2 Eliciting and Reporting Serious Adverse Events

The HCP will periodically assess subjects for the occurrence of SAEs. To avoid bias in eliciting SAEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All SAEs reported by the subject must be recorded on the source documents and data collection tool provided by the sponsor. Serious AE collection is to begin after a subject has signed the ICF. All SAEs will be collected starting from the signing of the ICF until 2 weeks following the last dose of CoE product.

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

In addition, Clinical Safety and Pharmacovigilance must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 5.3. Special attention should be paid to recording hospitalisation and concomitant medications.

5.3 Immediately Reportable Events

The HCP must immediately report after becoming aware of any SAE, potential DILI, confirmed pregnancy, or device-related nonserious AE requiring discontinuation of the DMS, by telephone, fax, or e-mail to Clinical Safety and Pharmacovigilance using the contact information on the cover page of this protocol (see also Appendix 2). An IRE form must be completed and sent by e-mail, fax, or overnight courier to Clinical Safety and Pharmacovigilance. (Please note that the IRE form is NOT the SAE form.)

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

5.4 Potential Drug-induced Liver Injury

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

5.5 Pregnancy

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

For FOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures to prevent pregnancy during the course of the trial and for 30 days after the last use of the DMS for females, and 90 days after the last use of the DMS for males. Unless the subject is sterile (eg, females who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm (barrier method), intrauterine device (barrier method), birth control pills, birth control depot injection, birth control implant, condom with spermicide (barrier method), or sponge with spermicide (barrier method). Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each HCP visit.

Before enroling FOCBP in this clinical trial, HCPs must review the guidelines about trial participation with all FOCBP. The topics should generally include:

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

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

A urine pregnancy test for human chorionic gonadotropin will be performed at screening on all FOCBP. If a urine test is performed and is positive, the HCP will follow-up with a confirmatory serum test.

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

If a female subject is suspected to be pregnant before the subject receives DMS, the DMS administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the DMS and must not be enroled in the trial. If pregnancy is suspected while the subject is taking DMS, the DMS

may be continued at HCP discretion until the result of the pregnancy test is known. If pregnancy is confirmed, the DMS may be continued at HCP discretion based on treatment guidelines for the medication administered. If the HCP discontinues the subject from DMS, it must be performed in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. (Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the Clinical Safety and Pharmacovigilance department [see the cover page of this protocol for contact information]).

The HCP must immediately notify the sponsor of any pregnancy associated with DMS exposure during the trial and for 30 days for a female subject, 90 days for female partner of a male subject, after the last dose of the DMS, and record the event on the IRE form and forward it to the sponsor. Pregnancies of subjects or their partners will be followed to term. In the event of pregnancy of a subject's partner, consent to follow the pregnancy will be obtained. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

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

5.6 Follow-up of Serious Adverse Events

This trial requires that subjects be actively monitored for SAEs up to 14 days after the last use of the DMS is administered.

Serious AEs that are **identified or ongoing at the last scheduled contact** must be recorded in the data collection tool and reported to the Clinical Safety and Pharmacovigilance department according to the reporting procedures outlined in Section 5.3. This may include **unresolved previously reported SAEs, or new SAEs.** The HCP will follow SAEs until the events are resolved, stabilised, or the subject is lost to follow-up. Resolution means that the subject has returned to the baseline state of health and stabilised means that the HCP does not expect any further improvement or worsening of the subject's condition. The HCP will continue to report any significant follow-up information to Clinical Safety and Pharmacovigilance up to the point the event has been resolved.

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

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

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

6 Statistical Analysis

Descriptive statistics will be presented for primary, secondary, and exploratory endpoints and safety variables.

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

6.1 Sample Size

The trial is exploratory in nature.

The sample size was determined from practical considerations. Approximately 60 subjects will be enroled in the trial. With an approximate 25% discontinuation rate, it is expected that at least 45 subjects will complete the 8-week assessment period of the trial.

6.2 Datasets for Analysis

The following analysis samples are defined for this trial:

- Enroled sample: All subjects who sign an ICF and enter the trial;
- Intent-to-treat (ITT) sample: All subjects who enter the trial and use the DMS;
- Safety sample: All subjects who enter the trial and use the DMS;

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

6.3 Handling of Missing Data

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

6.4 Primary, Secondary, and Exploratory Endpoint Analyses

The analysis will be conducted based on the ITT sample (ie, all subjects who enter the trial and use the DMS).

Descriptive statistics will be provided for all primary, secondary, and exploratory endpoints and safety variables in general. Continuous variables will be summarised by tabulations of mean, median, range, and SD. Tabulations of frequency distributions will be provided for categorical variables.

6.4.1 Primary Endpoint Analysis

The primary endpoint is the proportion of days with good patch coverage during the trial, which will be calculated by the number of days with good patch coverage divided by the total number of trial days for each subject.

The proportion of days with good patch coverage will be summarised by week and for overall trial period and the descriptive statistics include mean, SD, median, minimum, maximum, first quartile and third quartile.

6.4.2 Secondary Endpoint Analysis

The secondary endpoint is subject's adherence metric, which is the proportion of detected MITs over the expected MITs ingested during the trial days with good patch coverage and calculated as the number of ingested MITs detected divided by the number of expected MITs ingested during the trial days with good patch coverage for each subject.

The adherence metric will be summarised by week and for overall trial period and the descriptive statistics including mean, SD, median, minimum, maximum, and first quartile and third quartile.

6.4.3 Exploratory Endpoint Analyses

The exploratory endpoints are as follows:

1) To explore the acceptance and performance of the DMS with HCPs and adult subjects with SCH, schizoaffective disorder, or first episode psychosis as measured by:
   - The proportion of time during the trial period when the subject wears their patch. The time duration of patch wearing will be calculated based on the digital health data.
   - The level of engagement and satisfaction of subjects, HCPs, and caregivers/support persons (if applicable), as determined by surveys Subject Usability and Satisfaction Scale, HCP Utility Survey, and Caregiver/Support Person Involvement Scale [if applicable]) will be summarised using descriptive statistics, respectively. Tabulations of frequency distributions will be provided for all these categorical variables.
   - The proportion of days subjects are using the application and the proportion of days that HCP are using the HCP dashboard during the trial will be summarised using descriptive statistics.
   - The proportion of ingested MIT registered on the digital health data server versus expected MIT ingested will be summarised using descriptive statistics. The proportion is calculated as the number of MITs detected divided by the number of expected MITS ingested during the treatment period.
2) Additional variables will be captured to better understand outcomes that may impact use of the DMS or be impacted by the use of the DMS including:
   - Change from baseline to Week 8 in CGI-S will be summarised using descriptive statistics;
   - HCP visits and associated setting of care;
   - Details surrounding any hospitalisations;
   - Occurrence and timing of community/home visits;
   - Any referrals during the observation period.

Details of exploratory analysis will be included in SAP.

6.5 Analysis of Demographic and Baseline Characteristics

Demographic and baseline characteristics for enroled subjects will be summarised and listed by subject.

6.6 Safety Analysis

Safety analysis will be conducted based on the safety sample.

Safety variables to be analysed include SAEs, device-related nonserious AEs, and the suicidality assessment. Any product quality complaints will be analysed as required.

6.6.1 Adverse Events

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

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs potentially causally related to the DMS
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the DMS

Adverse event data will also be present in listings.

6.6.2 Clinical Laboratory Data

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

6.6.3 Physical Examination and Vital Signs Data

Not applicable.

6.6.4 Electrocardiogram Data

Not applicable.

6.6.5 Other Safety Data

6.6.5.1 Suicidality Assessment

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

7 Management of Digital Medicine System

7.1 Packaging and Labeling

The DMS will be provided to the HCPs and the persons designated by the HCP(s) or institution(s) by the sponsor or designated agent. The CoE products will be supplied in bottles. Each bottle used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information as required by local regulatory authorities.

The details of the contents of the DMS are provided in Appendix 3.

7.2 Storage

The CoE products and patches will be stored in a securely locked cabinet or enclosure. Access will be limited to HCPs and their designees. Neither HCPs nor any designees may provide medical device to any subject not participating in this protocol.

The medical device should be stored according to conditions specified in the label of the DMS. The HCP or designee will maintain a temperature log in the storage area recording the temperature at least once each working day.

7.3 Accountability

The HCP or designee must maintain an inventory record of the DMS (patches and drug originator tablet + CoE MIT) received, dispensed, administered, and returned.

7.4 Returns and Destruction

Upon completion or termination of the trial all unused and/or partially used CoE products and patches must be destroyed at the trial site(s) or designated agent.

The assigned HCP or designate will facilitate the destruction of unused and/or partially used CoE products and patches.

7.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a HCP, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device

after it is released for distribution. Examples include, but are not limited to, communications involving:

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

7.5.1 Eliciting and Reporting Product Quality Complaints

The HCP or designee must record all PQCs identified through any means from the receipt of the DMS from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The HCP or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below to Otsuka Pharmaceutical Europe Ltd. Quality Assurance (OPEL QA):

- Online - Send information required for reporting purposes to PPD

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

7.5.2 Information Required for Reporting Purposes

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

7.5.3 Return Process

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

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

7.5.4 Assessment/Evaluation

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

8 Records Management

8.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the HCPs and made available for direct inspection by authorised persons.

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

8.2 Data Collection

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

- Documentation of the informed consent process, including any revised consents;
- Documentation of the HCP's decision to enrol the subject into the trial, the review of all inclusion/exclusion criteria prior to the use of the DMS, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any SAEs and the HCP's assessment of relationship to the DMS must also be recorded;

- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Any changes to information in the trial progress notes and other source documents will be initialed and dated on the day the change is made by the HCP authorised to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician. If electronic data systems are being utilised, a full audit trail of changes must be maintained.

Data will be entered by the HCP into a data collection tool specific for this trial.

8.3 File Management at the Trial Site

The HCP will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The HCP/institution will take measures to prevent accidental or premature destruction of these documents.

8.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating HCPs maintain detailed clinical data for the longest of the following periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if DMS development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the HCP that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The HCP must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The HCP will be responsible to maintain adequate and accurate electronic or

hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the HCP withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

9 Quality Control and Quality Assurance

9.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all HCPs and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

9.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, the DMS supply, presence of required documents, the informed consent process, and comparison of the data collection tool with source documents. The HCP agrees to participate with audits.

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

10 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IEC according to regional requirements, and the HCP will provide that documentation to the

sponsor. The IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling the data collection tool, the HCP and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject ID code will be used to identify each subject.

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

11 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorised regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements.

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

12 Amendment Policy

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

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

13 Publication Authorship Requirements

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

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

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

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

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Appendix 1 Sponsor Personnel

PPD

Phone: PPD

E-mail: PPD

PPD

Phone: PPD

E-mail: PPD

PPD

Phone: PPD

PPD

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Appendix 2 Safety Reporting

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

Report Immediately Reportable Events (SAEs, potential DILI, confirmed pregnancies, and any device-related nonserious AEs) to the Global Safety and Pharmacovigilance department as follows:

Global Safety and Pharmacovigilance

Phone: PPD
Global Fax: PPD
Global E-mail: PPD

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Appendix 3 Digital Medicine System Contents

Digital Medicine System Contents	
Digital Medicine System Component	**Description**
CoE product	CoE product will be dispensed to the subjects during the trial. Capsules will be taken as prescribed by the healthcare professional, with approximately 120 mL of water.
Patch	Patches will be dispensed to a subject for use. Each patch is designed for 7-day wear; extra devices are provided should the subjects desire to change the patch more frequently during the period of familiarization or in case of sensor malfunction.
Computing Device & Accessories	Subjects will use their own smartphone and required accessories or the smartphone provided by the Sponsor. Subjects will be requested to carry their smartphone with them as much as possible and to plug in the device at a dedicated location at home where they could have easy and frequent access when not being carried. The preferred location is on a nightstand or a location immediately adjacent to where the subject sleeps.
Digital Medicine System Reference Guide	A printed reference guide will provide explicit directions for normal use and troubleshooting.

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Appendix 4 Subject Usability and Satisfaction Scale

Section A: Usability

1. How easy or difficult was it for you to apply the patch on your body?

Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
1	2	3	4	5	6	7

2. How easy or difficult was it to pair the patch with the mobile phone application (app)?

Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
1	2	3	4	5	6	7

3. How easy or difficult was it for you to use the mobile phone application (app)?

Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
1	2	3	4	5	6	7

4. How easy or difficult was it for you to use the Digital Medicine System?

Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
1	2	3	4	5	6	7

5. How well do you agree with the following statement?

- **In general, I did not mind wearing the patch.**

Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
1	2	3	4	5	6	7

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6. Since your last visit, did you receive assistance when changing and pairing the required patches? Yes No

If yes,

	Never	Once a month or less	A few times a month	Once a week	A few times a week	Daily
How much assistance did you receive when applying the patches?						
How much assistance did you receive when syncing the technology?						

If you did receive any help or assistance, who helped or assisted you?
(please place a √ [check] to indicate who helped or assisted you)

Friend	Hired Caregiver	Relative*	Other**

*If a relative helped or assisted you, then please specify their relationship to you (such as wife, husband, father, mother, sister, brother, or whatever else you think is the most appropriate description of the relative who helped you): _____

**If you selected "Other", please specify your relationship to the person who helped you

_____

Section B: Satisfaction

7. How easy or difficult was it for you to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?

Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
1	2	3	4	5	6	7

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8. How helpful or unhelpful was the Digital Medicine System in the management of your condition?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful
1	2	3	4	5	6	7

9. How helpful or unhelpful was the Digital Medicine System for sharing information with your healthcare professionals to help you understand your treatment plan?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful
1	2	3	4	5	6	7

10. How helpful or unhelpful was the Digital Medicine System in improving your discussions with your doctor / treatment team?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful
1	2	3	4	5	6	7

11. Based on your experience, how would you rate your satisfaction with the Digital Medicine System?

Extremely Dissatisfied	Dissatisfied	Somewhat Dissatisfied	Neutral	Somewhat Satisfied	Satisfied	Extremely Satisfied
1	2	3	4	5	6	7

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12. How likely would you be to use the Digital Medicine System in the future, if it were available and recommended by your doctor?

Extremely Unlikely	Unlikely	Somewhat Unlikely	Neutral	Somewhat Likely	Likely	Extremely Likely
1	2	3	4	5	6	7

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Appendix 5 Healthcare Professional Utility Survey

We ask the HCP at a trial site/trust to complete this survey for each subject enroled. Please answer the below questions based on your overall experience using DMS.

1. How easy or difficult was it for you and your subject to apply the patch on the subject's body?

	Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
	1	2	3	4	5	6	7
For you							
For your **subject**							

2. How easy or difficult was it for you and your subject to sync the patch with the mobile phone application (app)?

	Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
	1	2	3	4	5	6	7
For you							
For your **subject**							

3. How easy or difficult was it for you and your subject to complete the overall onboarding for the Digital Medicine System?

	Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
	1	2	3	4	5	6	7
For you							
For your **subject**							

4. Overall, how easy or difficult was it for you and your subject to use the mobile phone application (app)?

	Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
	1	2	3	4	5	6	7
For you							
For your **subject**							

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5. Overall, how easy or difficult was it for you and your subject to use the entire Digital Medicine System, which includes the patch, pills, and mobile phone application (app)?

	Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
	1	2	3	4	5	6	7
For you							
For your **subject**							

6. How easy or difficult was it for you to use the HCP dashboard?

Extremely Difficult	Difficult	Somewhat Difficult	Neutral	Somewhat Easy	Easy	Extremely Easy
1	2	3	4	5	6	7

7. How helpful or unhelpful do you think the Digital Medicine System was for the following elements of clinical management you experienced in the study?

	Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful
	1	2	3	4	5	6	7
Assessment							
Clinical Advice/ Recommenda-tions							
Treatment Decisions							

8. How effective was the Digital Medicine System in aiding decision-making for medication adherence?

Extremely Not Effective	Not Effective To Use	Somewhat Not Effective To Use	Neutral	Somewhat Effective To Use	Effective To Use	Extremely Effective To Use
1	2	3	4	5	6	7

9. How helpful or unhelpful was the Digital Medicine System in providing a way to better engage your subjects in self-management of their condition?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful
1	2	3	4	5	6	7

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10. How helpful or unhelpful was the Digital Medicine System in improving quality of care for your subject?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful
1	2	3	4	5	6	7

11. How helpful or unhelpful was the Digital Medicine System in improving your conversations with your subject about their treatment plan and progress?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful
1	2	3	4	5	6	7

12. How helpful or unhelpful was the Digital Medicine System in the identification of potential lifestyle changes for your subject (eg, sleep and exercise)?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful
1	2	3	4	5	6	7

13. Other than during the subject visit(s), did you look at the HCP dashboard at other times? Please select all that apply

	Place a √ (tick) next to the time you referred to the HCP dashboard
No, only during the subject visit	
Prior to subject visit (same day as visit)	
In between visits	
Other: *Please Specify:* _____	

14. What features did you find helpful? Please select all that apply

	Place a √ (check) next to the features you found helpful	For the features you have selected, please rank these features from 1 (most helpful) to 7 (least helpful) in order of helpfulness
Pill ingestion data		
Subject reported reason code for missed doses		
Missed dose alerts		
Activity		
Rest		
Subject reported rest quality rating		
Other: *Please Specify:* _____		

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15. Did you setup alerts to be notified of missed doses? Yes/no

a. If yes, based on your overall experience, how helpful were the missed dose alerts?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful	Not Applicable – No Alerts Received
1	2	3	4	5	6	7	

15a. If you received a missed dose alert what action did you take, if any? (If none, please write N/A) _____

16. Did you setup alerts to be notified of missed doses? Yes/no

a. If yes, based on your overall experience, how helpful were the multiple dose alerts?

Extremely Unhelpful	Unhelpful	Somewhat Unhelpful	Neutral	Somewhat Helpful	Helpful	Extremely Helpful	Not Applicable – No Alerts Received
1	2	3	4	5	6	7	

16a. If you received a multiple dose alert what action did you take, if any? (If none, please write) N/A _____

17. How well do you agree with the following statement?

a. Overall, the Digital Medicine System adds value to my practice.

Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
1	2	3	4	5	6	7

18. Based on your overall experience with this subject, how would you rate your satisfaction with the Digital Medicine System?

Extremely Dissatisfied	Dissatisfied	Somewhat Dissatisfied	Neutral	Somewhat Satisfied	Satisfied	Extremely Satisfied
1	2	3	4	5	6	7

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Appendix 6 Caregiver/Support Person Involvement Scale

DMS Caregiver/Support Person Involvement Scale

1. **Are you aware that the study participant/subject is currently participating in the Digital Medicine study (check one)?**

Yes	No *

*if no, stop here and do not answer the rest of the questions on this form.

2. **Indicate your relationship to the study participant/subject by placing a √ (check).**

Friend	Hired Caregiver	Relative*	Other**

*If you are a relative, please specify relationship to the study participant/subject, eg., wife, father:

**If you selected "Other", please specify your relationship to the study participant/subject:

_____

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3. How much involvement did you provide the subject with regard to taking medication, pairing the patch, applying the patch, and using the app during the course of the study?

	Never	Once a month or less	A few times a month	Once a week	A few times a week	Daily
How much overall assistance did you provide the subject during the course of the study?						
How much assistance did you provide with patch application?						
How much assistance did you provide with syncing the technology?						
How much assistance did you provide with using the app?						
	Never	**Once a week**	**A few times a week**	**Nearly every day**	**Daily**	**More than once/day**
How much overall assistance did you provide during the past week of the study?						

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Appendix 7 Patient Activation Measure-Mental Health Scale

PAM-MH 13

The following questions ask about your feelings regarding your mental healthcare.

When you think about for mental health and mental health care, how much do you agree or disagree with the following statements? Please circle the answer that you most agree with:

1. When all is said and done, I am the person who is responsible for managing my mental health.

1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

2. Taking an active role in my own mental health is the most important factor in determining my mental health and ability to function.

1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

3. I am confident that I can take actions that will help prevent or minimize some symptoms or problems associated with my mental health condition.

1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

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4. I know what each of my prescribed mental health medications does.			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

5. I am confident that I can tell when I need to go get mental health care, and when I can handle a mental health problem myself.			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

6. I am confident I can tell my mental health clinician about concerns I have, even when he or she does not ask.			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

7. I am confident that I can follow through on mental health treatments I need to do at home.			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

8. I understand the nature and causes of my mental health condition(s).			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

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9. I know the different treatment options available for my mental health condition(s).			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

10. I am able to maintain the lifestyle changes I have made for my mental health.			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

11. I know how to prevent further mental health problems.			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

12. I am confident I can figure out solutions when new situations or problems arise with my mental health.			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

13. I am confident that I can maintain lifestyle changes, like diet and exercise, even during times of stress.			
1	2	3	4
Strongly Disagree	Disagree	Agree	Strongly Agree

Appendix 8 Clinical Global Impression-Severity of Illness Scale

Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?

0 = Not assessed

1 = Normal, not at all ill

2 = Borderline mentally ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill subjects

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Appendix 9 Personal and Social Performance Scale

Personal and Social Performance Scale (PSP)

The rating is based on four main areas: (a) socially useful activities, including work and study; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors.

Data will be captured in the following format using the PSP descriptions provided below:

	Absent	Mild	Manifest	Marked	Severe	Very Severe
a. Socially useful activities, including work and study	☐	☐	☐	☐	☐	☐
b. Personal and social relationships	☐	☐	☐	☐	☐	☐
c. Self-care	☐	☐	☐	☐	☐	☐
d. Disturbing and aggressive behaviors	☐	☐	☐	☐	☐	☐

The levels of functioning in other areas should be taken into account to adjust the rating inside the decimal level (for instance, from 31 to 40). Suicidal risk is not included in the scale.

10-point intervals	PSP descriptions
100-91	Excellent functioning in all four main areas*. He/she is held in high consideration for his/her good qualities, copes adequately with life problems, is involved in a wide range of interests and activities
90-81	Good functioning in all four main areas, presence of only common problems or difficulties
80-71	Mild difficulties in 1 or more of areas a-c
70-61	Manifest, but not marked difficulties in 1 or more areas a-c, *or* mild difficulties in d
60-51	Marked difficulties in 1 of areas a-c, *or* manifest difficulties in d
50-41	Marked difficulties in 2 or more, *or* severe difficulties in 1 of areas a-c, with or without manifest difficulties in d
40-31	Severe difficulties in 1 *and* marked difficulties in at least 1of areas a-c, *or* marked difficulties in d
30-21	Severe difficulties in 2 of areas a-c, *or* severe difficulties in d, with or without impairment in areas a-c
20-11	Severe difficulties in all areas a-d, *or* very severe in d with or without impairment in general areas a-c. If the person reacts to external prompts the suggested scores are 20-16; if not, the suggested scores are 15-11.
10-1	Lack of autonomy in basic functioning with extreme behaviors but without survival risk (ratings 6-10) or with survival risk, eg, death risk due to malnutrition, dehydration, infections, inability to recognize situation of manifest danger (ratings 5-1).

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For main areas a-c, the degrees of severity are:	
Absent	
Mild	Not manifest difficulties, known only to someone who is very familiar with the person
Manifest, but not marked	Difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area, given the person's socio-cultural context, age, sex and educational levels
Marked	Difficulties heavily interfering with role performance in that area; however, the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able to reach the previous level of functioning
Severe	Difficulties that make the person unable to any role performance in that area, if not professionally helped, or lead the person to a destructive role; however, there are no survival risks.
Very severe	Impairments and difficulties of such intensity to endanger person's survival.

For general area d, the degrees of severity are:	
Absent	
Mild	Mild rudeness, unsociability or whingeing
Manifest, but not marked	Speaking too loudly or speaking to others in a too-familiar manner, or eating in a socially unacceptable manner
Marked	Insulting other in public, breaking or wrecking objects, acting frequently in a socially inappropriate but not dangerous way (eg, stripping in public or urinating in public).
Severe	Frequent verbal threats or frequent physical assaults, without intention or possibility of severe injuries.
Very severe	Frequent aggressive acts, aimed at or likely to cause severe injuries.

Occasional is defined as occurring three or more times in the reference period or occurring even less than three times but in circumstances and/or with such a previous history to convince the rater that there is a risk of recurrence in the near future. If the aggressive behavior has been present occasionally, the rating may be decreased by one degree, eg, from severe to marked.

* Main areas: a=socially useful activities, including work and study; b=personal and social relationships; c=self-care; d=disturbing and aggressive behaviors.

Guidelines for PSP Total Score

Ratings from 71-100 reflect only mild difficulties.

Ratings from 31-70 reflect manifest disabilities of various degrees.

Ratings from 1-30 reflect functioning so poor that intensive support or supervision is needed.

Morosini, P.L., Magliano, L., Brambilla, L., Ugolini, S., Pioli, R. (2000). Development, reliability, and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatrica Scandinavica 101*(4), 323-329.

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Appendix 10 Skin Irritation Scoring System

Dermal Response:

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

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

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Agreement

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

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the Digital Medicine System, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where Digital Medicine System will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

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

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

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

_____	_____	_____
Healthcare Professional Print Name	Signature	Date

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