- **Protocol number: 031-201-00186**
- **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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Statistical Analysis Plan for Protocol 031-201-00186

Otsuka Pharmaceutical
Development & Commercialization, Inc.

Medical Device

STATISTICAL ANALYSIS PLAN
for
Protocol No. 031-201-00186
EudraCT No. 2017-004602-17

A Multicenter, 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)

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1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data collected under the clinical protocol 031-201-00186, dated 01 Dec 2017.

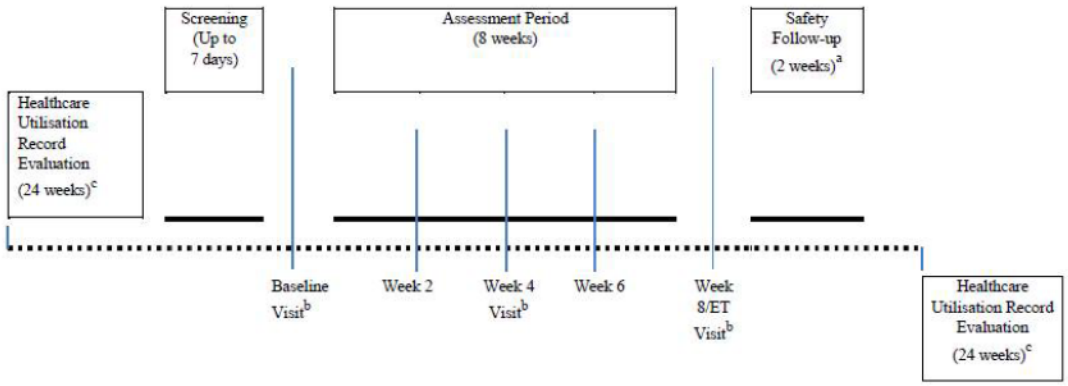
2 Trial Objectives

The primary objective of this trial is to 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 on an oral atypical antipsychotic (aripiprazole, olanzapine, quetiapine, or risperidone).

3 Trial Design

3.1 Type/Design of Trial

This is a multicentre, 8-week, single-arm, open-label, pragmatic trial. 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).Trial Design Schematic is provided in Figure 3.1-1.



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

Subjects in this trial 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 study includes the following visits:

Screening/Baseline Visit (Days -7 to -1): After providing the informed consent, subjects 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.

Assessment Period (8 weeks):
Initiation of the DMS commences 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 visit the HCP for clinical evaluations at Week 4;
- Subjects collect their DMS prescription refill at Week 4 visit for next 4 weeks until Week 8/ET visit;
- Subjects visit the HCP at Week 8/ET and undergo another clinical evaluation.

Safety and tolerability data are to 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 are monitored on the technology by the HCPs, who 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 are to be collected.
Follow-up:
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). Following the Week 8/ET visit, the subjects don't use the DMS and return to standard care (routine follow-up from care teams and continue non-DM medications). A safety follow-up phone call occurs at 2 weeks after the Week 8/ET visit, which are to be the last official subject contact.

4 Sample Size and Power Justification

The trial is exploratory in nature. The sample size was determined from practical considerations. Approximately 60 subjects will be enrolled 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.

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5 Statistical Analysis Datasets

5.1 Data Sets Analyzed

The following analysis samples are defined for this trial:

- Enrolled Sample: All subjects who sign an informed consent form and enter the trial.
- Safety Sample: All subjects who enter the trial and use the Digital Medicine System (DMS).
- Intent-to-treat (ITT) 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. It is noted that the Safety Sample and the ITT Sample are the same in this trial. Analyses of the safety data will be based on the Safety Sample.

5.2 Definition of Baseline and Last Visit

In general, the baseline evaluation is defined as the last available measurement prior to the first dose of Investigational Medicinal Product (IMP) at the baseline visit (or during screening if such evaluation is not available at baseline). If the date is present and the time is unknown for the first dose of IMP or the baseline evaluation, the last available measurements on (or prior to) the first dose date will be deemed as baseline. This definition of baseline is applicable to all analyses unless otherwise specified.

Last visit is defined as the last scheduled clinic visit (including the early termination visit) at which the subject's last evaluation is performed.

5.3 Trial Week/Month Windows

Trial Week/Month is derived by mapping Trial Days into corresponding time windows as specified in Table 5.3-1. Trial Day is derived as: Trial Day = Date of assessment - Date of the 1st use of DMS + 1. If there are multiple observations within the same week, only the last observation within that week is used for the summary tables. The time window mapping rules are applicable to all data that are reported by scheduled week unless otherwise stated.

Table 5.4.1-1 Mapping of Trial Weeks

Trial Week/Month	Target Day	Day Range
Baseline	1	<=1
Week 2[a]	15	2~22
Week 4	29	23~36
Week 6[a]	43	37~50
Week 8	57	51-64

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[a]Not applicable to the subject. HCP will review dashboard only

5.4 Missing Data

5.4.1 Missing Data Handling

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.

5.4.2 Incomplete Dates

Unless otherwise stated in the analysis sections (e.g., AE and concomitant medication), the general rule for imputing incomplete dates when the year is present is to use January if only the month is missing and the first day of a month if only the day is missing. If both month and day are missing but the year is available, January 1 is imputed. If the year is unknown, the date will be considered as missing.

6 Primary and Secondary Outcome Variables

6.1 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, which is calculated as the date of the last dose of trial medication - date of the first dose of trial medication plus 1 for that particular duration. If a subject is taking a drug holiday at investigator's decision, those days will be excluded from the denominator. The good patch coverage will be defined as having at least 80% patch data available or IEM (within a MIT)/MIT detected within the 24-hour period for each day while the subject is on the trial.

6.2 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.

6.3 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. If a subject is taking a drug holiday at investigator's decision, those days will be excluded from the denominator.
   - 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. If a subject is taking a drug holiday at investigator's decision, those days will be excluded from the denominator.
2) Additional variables will be captured to better understand outcomes that may impact use of the DMS or be impacted using 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 hospitalizations;
   - Changes in Patient Activation Measure-Mental Health (PAM-MH)
   - Occurrence and timing of community/home visits;
   - Cost and time implications of any interventions;
   - Any referrals during the observation period.

7 Summary of Trial Data

7.1 Disposition of Subjects

The number of subjects enrolled into the trial, the number of subjects who have used any component of DMS, the number of subjects who enter the assessment period and the number of subjects, who discontinue from the trial during assessment period, together with reasons for discontinuation taken from the eCRF completion status page, will be tabulated for all subjects.

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7.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics for enrolled and ITT Sample subjects will be summarized and listed by subject. Summary statistics for demographic and baseline disease characteristics are calculated (by gender) for all subjects enrolled in the trial. Demographic characteristics include age, gender, childbearing potential, race, ethnicity, (body weight, height, BMI, if available), marital status, employment status and baseline disease characteristics include duration of disease (for example, time since first diagnosis of SCH), Patient Activation Measure-Mental Health (PAM-MH) Scale, Clinical Global Impression – Severity scale (CGI-S) and Personal and Social Performance (PSP) scale total score. Summary statistics will consist of mean, median, minimum, maximum, and standard deviation (SD) for continuous variables and tabulations of frequency distributions for categorical variables. Summary statistics for demographic and baseline disease characteristics will be provided for each disease type and the overall Enrolled Sample, respectively. In addition, Summary statistics for demographic and baseline disease characteristics could be provided by site for the ITT Sample. The demographic characteristics of caregivers will be summarized too if applicable.

Time since first diagnosis of SCH is calculated as (date of screening assessment - date of first diagnosis + 1)/365.25. Partial first diagnosis date will be handled by the rules specified in Section 5.4.2.

7.3 Prior and Concomitant Medication

The proportion of subjects taking concomitant medications will be tabulated by drug classification using the B2 Enhanced version of WHO-DDE B2 (March 2013) for all Safety Sample for 3 periods, i.e. prior to, during and after the DMS use.

In addition, listings of concomitant mediations will be provided.

7.4 Protocol Deviations

Protocol deviations will be summarized by center and type of deviation. Protocol deviations data will be summarized by type of deviations (e.g., deviations in entry criteria, dosing, concomitant medication, procedural, etc.). In addition, a subject listing will be provided describing the deviations for each subject.

8 Usability and Satisfaction Endpoint Analyses

Descriptive statistics will be provided for all primary, secondary, and exploratory endpoints and safety variables in general. Continuous variables will be summarized by tabulations of n, mean, median, range, and standard deviation (SD). Tabulations of frequency distributions (i.e., n (%)) will be provided for categorical variables.

8.1 Primary Endpoint Analyses

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 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.

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

The analysis will be conducted based on the intent-to-treat (ITT) sample (i.e., all subjects who enter the trial and use the DMS) and will also be summarized by disease type.

8.2 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 summarized by week and for overall trial period and the descriptive statistics including mean, SD, median, minimum, maximum, and first quartile and third quartile. The adherence will also be summarized by disease type.

8.3 Exploratory Endpoint Analysis

The exploratory endpoints analyses are as follows.

- The proportion of time during the trial period when the subject wears their patch is calculated as the time during the trial period when the subject wears their patch divided by the treatment duration and will be summarized by week and for overall trial period and the descriptive statistics including n, mean, SD, median, minimum, maximum, and first quartile and third quartile. The time duration of patch wearing will be calculated based on the digital health data. Treatment duration will exclude the period that the subject took a drug break at investigator's decision. In addition, subject patch wearing time which is defined as number of subject waring at least one patch over the total subject will be summarized by disease type, site over time.

- 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 summarized using descriptive statistics, respectively. Tabulations of frequency distributions (i.e., n (%)) 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 summarized using descriptive statistics including n, mean, SD, median, minimum, maximum, and first quartile and third quartile.

- The proportion of ingested MIT registered on the digital health data server versus expected MIT ingested will be summarized using descriptive statistics n, mean, SD, median, minimum, maximum, and first quartile and third quartile. The proportion will be calculated as the number of MITs detected (registered on digital health data server) divided by the number of expected MITS ingested during the treatment period (expected number of treatment days in the trial or summarized period).

- Subjects' feeling of their mental health will be rated using four-point response in PAM-MH scale at screening/baseline and Week 8/ET visit. CGI-S severity score (range 1-7) is single item rating scores, with higher scores representing greater severity or less improvement. The change in PAM-MH and CGI-S score will be summarized by descriptive statistics using the ITT sample. Descriptive statistics include mean, median, minimum, maximum and standard deviation (SD). For the analysis of change from baseline, only the subjects with both baseline and at least 1 post-baseline assessment will be included.
- Tabulations of frequency distributions (i.e., n (%)) of subjects will also be provided for HCP visits and associated setting of care, details surrounding any hospitalizations, occurrence and timing of community/home visits and any referrals during the assessment period.

8.4 Other Assessments:

8.4.1 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. This scale also measures whether any disturbing or aggressive behaviors are present. A global score of general functioning will also be obtained using this scale. The PSP total score will be summarized by tabulations of n, mean, median, range, and standard deviation (SD) in baseline characteristics.

8.4.2 Call Centre Data

The call center data will not be included in the study report.

9 Safety Analyses

The safety endpoint of this trial is the safety and tolerability of the DMS system, as assessed by the frequency and severity of AEs, device-related AEs, SAEs, AEs leading to discontinuation, and unanticipated adverse device effects.

Safety analysis will be conducted based on the Safety Sample, and safety variables to be analyzed include AEs and clinical laboratory tests if applicable. In addition to the analysis of standard safety parameters, suicidality will be evaluated through analysis of data from appropriate scales.

9.1 Adverse Events

Device-associated AEs are those events reported on the adverse device event page of the CRF. All medication-associated AEs and device-associated AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA version 19.0) preferred term (PT). A treatment-emergent AE (TEAE) is defined as an AE that starts after the first use of medication-device, or an AE that continues from baseline (before using the device) and becomes serious, or trial treatment related, results in death, or leads to discontinuation, interruption of device use. An AE with an unknown start date will be considered as a TEAE. All AEs will be summarized by drug taken and overall.

The incidences of the following categories of treatment emergent AEs (TEAEs) will be summarized for the medication-associated and device-associated TEAEs, respectively:

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

For TEAEs related to patch, skin irritation scores will be assessed. The incidence of the skin irritation will be summarized by irritation grade for the subjects with patch-related TEAEs.

In addition, deaths, SAEs, AEs leading to discontinuation from the trial or trial treatment, suicide /suicidal ideation related AEs and patch-related TEAEs (with skin irritation scores) will be listed by subject for the Safety Sample.

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9.2 Clinical Laboratory Tests

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. Pregnancy laboratory data at screening will be listed by subject.

9.3 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. The number of times will be determined by number of face-to-face visits at the HCPs discretion. Sign of Suicidality if exhibited will be listed by subject.

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