Statistical Analysis Plan

Confirmatory Study of DSP-5423P in Patients with Schizophrenia
<Phase 3>

Protocol number: D4904020

Sumitomo Dainippon Pharma, Co., Ltd.

Version: 2
Date: 10JAN2018

Prepared by:

[redacted]

10 Jan 2018

Study Biostatistician, [redacted]
Statistician, Biostatistics Group, Data Science

Date

Approved by:

[redacted]

10 Jan 2018

Head of Biostatistics, [redacted]
Group Manager, Biostatistics Group, Data Science

Date

[redacted]

10 Jan 2018

Medical Lead, [redacted]
Fellow, Regional Functional Head of CNS Research

Date

[redacted]

11 Jan 2018

Head of Clinical Pharmacology, [redacted]
Group Manager, Clinical Pharmacology, Clinical Research

Date

Version History

Draft Versions	Version Date	Author
Client Draft 1.0	JUL 02, 2015	[redacted]
Client Draft 2.0	DEC 15, 2015	[redacted]
Client Draft 3.0	MAR 23, 2016	[redacted]
Client Draft 4.0	APR 05, 2016	[redacted]
Draft 5	NOV 24, 2016	[redacted]

Version	Study Biostatistician	Approval date	Head of Biostatistics/ Medical Lead/ Head of Clinical Pharmacology	Reason of changes
1	[redacted]	22DEC2016	[redacted]	First version
2	[redacted]	10JAN2018	[redacted]	General revisions. No major changes were made for methodology of primary efficacy analysis.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded Review Meeting
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CGI	Clinical Global Impression scale
CGI-S	Clinical Global Impression scale - Severity
CI	Confidence Interval
CK	Creatine phosphokinase
Cl	Chloride
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
DIEPSS	Drug-Induced Extrapyramidal Symptoms Scale
DSP	Dainippon Sumitomo Pharma
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EPS	Extra Pyramidal Symptoms
H	High
HbA1c	Hemoglobin A1c
ID	Identifier
K	Potassium
L	Low
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
MAPLV	Markedly Abnormal Post-Baseline Laboratory Values
MAPVS	Markedly Abnormal Post-Baseline Vital Signs
MAX	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligram
Min	Minimum
mITT	modified Intention-To-Treat
MMRM	Mixed Model for Repeated Measurements
N	Number of Subjects
Na	Sodium
NA	Not Applicable
NSW	New South Wales
PANSS	Positive and Negative Syndrome Scale

PD	Protocol Deviation
PK	Pharmacokinetic
PLCB	Placebo
PP	Per-Protocol
PT	Preferred Term
QC	Quality Control
QTc	QT interval corrected for heart rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment Emergent AE
TFL	Tables, Figures and Listings
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organisation
γ-GTP	γ-Glutamyltranspeptidase

1 SOURCE DOCUMENTS

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	02-Feburuary-2017	2.02
eCRF	10-November-2014	2.0

2 PROTOCOL DETAILS

2.1 Study Objectives

Primary:

The primary objective of the study is to evaluate the efficacy of DSP-5423P (40 and 80 mg/day) compared with placebo in patients with schizophrenia by assessing the mean change in Positive and Negative Syndrome Scale (PANSS) total score from baseline at Week 6.

Secondary:

The secondary objectives are to evaluate the safety of DSP-5423P compared with placebo for 6-week treatment, the long-term safety and efficacy of DSP-5423P, and the pharmacokinetics of DSP-5423P in patients with schizophrenia.

2.2 Overall Study Design

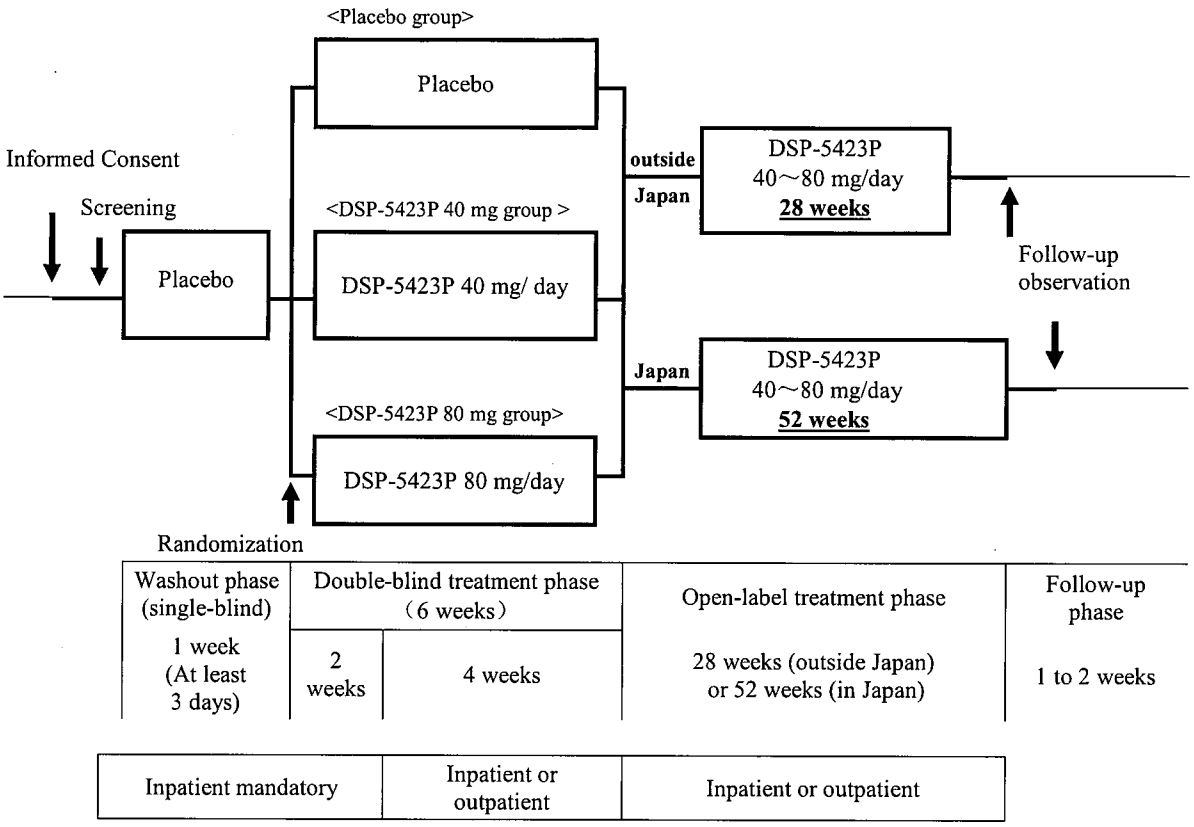
This study has two main phases:

1. Double-blind treatment phase: Multicenter, randomized, double-blind, placebo-controlled, parallel-group design

2. Open-label treatment phase: Multicenter, open-label, flexible dose design

The flowchart for this study is given in Figure 1.

Figure 1: Study Flowchart



The study consists of 4 phases: the washout phase, the double-blind treatment phase, the Open-label treatment phase, and the follow-up phase.

In the washout phase, placebo will be applied once daily for 1 week (at least 3 days) in a single-blind manner. After the washout phase, subjects will be randomized to one of three treatments: 40 mg of DSP-5423P, 80 mg of DSP-5423P, and placebo, at 1:1:1 ratio in the Double-blind treatment phase. The study drugs will be applied once daily for 6 weeks. Subjects who completed the double-blind treatment phase can enter the Open-label treatment phase. In the open-label treatment phase, DSP-5423P will be applied as flexible dose (40, 60, or 80 mg) once daily for 28 weeks (outside Japan) or 52 weeks (in Japan).

Subjects who completed the open-label treatment phase or who prematurely discontinued the study drug after entering the double-blind treatment phase will undergo the follow-up assessments in 1 to 2 weeks after the termination of the study drug.

2.3 Sample Size and Power

Double-blind treatment phase:

The target number of randomized subjects is 501.

DSP-5423P 40 mg group 167
DSP-5423P 80 mg group 167
Placebo group 167

The sample size for the study was determined by a Monte-Carlo simulation using Statistical Analysis Software (SAS Version 9.3, SAS Institute). The sample size calculation was based on the number of subjects required for the primary analysis in the modified intention-to-treat (mITT) population, where the primary analysis is to be performed on the change in PANSS total score from baseline at Week 6. The Hochberg procedure will be utilized to adjust multiple comparisons between each DSP-5423P (40 and 80 mg/day) group and the placebo group.

Based on the results of a previous double-blind placebo control study using DSP-5423 (1), the effect size was estimated to be 0.650 for DSP-5423 5 mg/day and 0.667 for DSP-5423 10 mg/day. It is expected that changes in PANSS total score will be smaller in the current study. This is due to patients with new exacerbated psychotic state will be enrolled as opposed to only patients hospitalized within two weeks from acute aggravation of schizophrenia in the earlier study. In addition, the drug-placebo differences in schizophrenia have been documented to decrease over time (2). For the reasons noted above, the effect size in the current study is assumed to be 0.45 which is about two-thirds of the effect size of DSP-5423 5 mg/day and DSP-5423 10 mg/day. A sample size of 133 per group was estimated to yield a complete power (probability of rejecting 2 null hypotheses) of 89% with a two-sided 5% significance level using the Hochberg procedure for multiplicity adjustment for two comparisons and taking an interim analysis for futility into consideration. Considering that there is the possibility

of subjects discontinuing before completion of the double-blind treatment phase, the total sample size will need to be 501 subjects or 167 subjects per treatment group.

3 EFFICACY AND SAFETY VARIABLES

3.1 Primary Efficacy Endpoint(s)

Mean change in PANSS total scores from baseline at Week 6, testing superiority of DSP-5423P (40 or 80 mg/day) over placebo.

3.2 Secondary Efficacy Endpoints

- Mean change in PANSS subscale scores (positive, negative, and general psychopathology) from baseline at Week 6
- Mean change in PANSS five-factor model scores (3) from baseline at Week 6
- Mean change in Clinical Global Impressions – Severity of Illness (CGI-S) score from baseline at Week 6
- Mean change in PANSS total score from the last evaluation before the initial application of DSP-5423P at each visit
- Mean change in PANSS subscales (positive, negative, and general psychopathology) from the last evaluation before the initial application of DSP-5423P at each visit
- Mean change in PANSS five-factor models from the last evaluation before the initial application of DSP-5423P at each visit
- Proportion of subjects who achieve a response, defined as 20% or greater improvement from baseline in PANSS total score at Week 6
- Mean change in CGI-S score from the last evaluation before the initial application of DSP-5423P at each visit
- Time to treatment discontinuation from initial application in the open-label treatment phase

3.3 Safety Variables

- Adverse events (AEs) and adverse drug reactions (ADRs)
- Extrapyramidal AEs and ADRs
- Skin-related AEs and ADRs at the application site
- Assessment of skin irritation reaction at the application site
- Mean change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total score (excluding overall severity) from baseline at Week 6
- Mean change in individual DIEPSS scores from baseline at Week 6
- Mean change in DIEPSS total score (excluding overall severity) from the last evaluation before the initial application of DSP-5423P at each visit

- Mean change in individual DIEPSS scores (excluding overall severity) from the last evaluation before the initial application of DSP-5423P at each visit
- Serum prolactin concentration
- Electrocardiogram (ECG) parameters (QTc)
- Concomitant use of antiparkinson drugs
- Assessment of suicide using Columbia-Suicide Severity Rating Scale (C-SSRS)
- Laboratory test values, vital signs, and body weight

4 PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

- Plasma concentrations of blonanserin
- Plasma concentrations of metabolite M-1 (N-de-ethylated metabolite).

5 ANALYSIS POPULATIONS

Analysis populations for the double-blind treatment phase will be determined by blinded data review meeting(s) before the database lock for the double blind treatment phase. Analysis populations for the open-label treatment phase and the DSP-5423P treatment period will also be determined prior to the initial statistical analysis for the open-label treatment phase.

5.1 Modified intention-to-treat population (mITT population)

The mITT population will consist of all subjects who meet all the following:

- Subjects who are randomized and apply the study drug at least once in the double-blind treatment phase.
- Subjects who have baseline and at least one post-baseline PANSS total score rated in the double-blind treatment phase.

5.2 Per-protocol population (PP population)

The PP population will consist of subjects of the mITT population who meet all the following:

- Subjects who meet the inclusion criteria at screening (1) to (4), and (7) and do not meet any of the exclusion criteria at screening (12) to (17), and (22)
- Subjects who meet all of the inclusion criteria at randomization and do not meet the exclusion criterion at randomization (1)
- Subjects who apply at least 80% of the study treatment in the double-blind treatment phase
- Subjects who receive no antipsychotics during the washout phase and the double-blind treatment phase

- Subjects who have no other important protocol deviations with an impact on the efficacy analyses as determined by a blinded data review

5.3 Open-label population

The open-label population will consist of all subjects who apply DSP-5423P at least once in the open-label treatment phase.

5.4 Safety population

The safety population will consist of all subjects who are randomized and apply the study drug at least once during the study.

5.5 DSP-5423P dosed population

The DSP-5423P dosed population will consist of all subjects who apply DSP-5423P at least once during the study. It does not include placebo group subjects who did not apply any DSP-5423P in the open-label treatment phase.

5.6 Pharmacokinetic analysis population (PK population)

The PK population will consist of all subjects who meet all the following:

- Subjects who are randomized and apply DSP-5423P at least once during the study
- Subjects who have at least one plasma concentration of blonanserin after application of DSP-5423P

5.7 Special Subpopulations

Not applicable.

6 DATA HANDLING

6.1 Day 1

Day 1 is defined as the day of the initial application in the double-blind treatment phase. Relative days after Day 1 are calculated as (date of assessment date – date of Day 1) + 1. Relative days prior to Day 1 are calculated as (date of assessment – date of Day 1). The day before Day 1 is Day -1.
Day 1 is also referred as the initial application date of double-blind treatment phase. The day of final application in the double-blind treatment phase will be referred as the final application date of double-blind treatment phase.

6.2 On-treatment Day 1

On-treatment Day 1 is defined as the day of the initial application of DSP-5423P in this study. Relative days after On-treatment Day 1 are calculated as (date of assessment date – date of On-treatment day 1) + 1. Relative days prior to On-treatment Day 1 are calculated as (date of assessment – date of On-treatment Day 1). The day before On-treatment Day 1 is On-treatment Day -1.
On-treatment Day 1 is also referred as the initial application date of DSP-5423P treatment period. The day of final application of DSP-5423P will be referred as the final application date of DSP-5423P treatment period.

Note that "On-treatment day X" is the same as "Day X" in the 40 mg and 80 mg group. For the placebo group however, "On-treatment day 1" is the first day of receiving an active treatment in the open-label treatment phase and "Day 1" is the first day in the double-blind treatment phase. In general, "Day X" is used for analysis for the double-blind treatment phase. "On-treatment day X" is used for analysis for the DSP-5423P treatment period and specifically excluded the double-blind treatment phase data: for subjects in the placebo group.

6.3 Analysis visits, baseline, and post-baseline measures

All data will be organized and analyzed according to the scheduled timing as outlined in Table 4 to Table 6 Schedule of Assessments and according to the visit denoted in the CRFs. Unscheduled visits may be used if scheduled visits are not available, as specified below. The data collected at the discontinuation visit within 7 days from the final application of study drug will be mapped to the next scheduled visit of the actual discontinuation date, as specified below.

Follow to assign analysis visit;
1. Decide post-base line measures,
2. Assign scheduled visit denoted in the CRFs,
3. Assign CRF discontinuation visits,
4. Assign CRF unscheduled visits, when applicable.

A. Double-blind treatment phase
   (i) Baseline analysis visit
   Defined as the last non-missing data of CRF Screening or CRF Day 1 (Baseline) visit on or before Day 1. Unscheduled visits will not be used.

(ii) Post-baseline data

Defined as the non-missing data on Day 1 through 7 days after the final application of study drug except for Screening and Day 1 (Baseline) visit. Data assessed on Day 1 and captured in the CRF visits of Week 1, discontinuation, and unscheduled visits will be considered as post-baseline data. Data assessed on Day 1 and captured in the CRF visits of Screening and Day 1 (Baseline) will NOT be considered as post-baseline data.

(iii) Post-baseline analysis visit

The post-baseline data will be mapped to post-baseline analysis visits, ie, Week 1, 2, 4, and 6 as follows:

(1) CRF Week 1, 2, 4, and 6 will be mapped to the corresponding analysis visits, regardless of the actual day of assessment.

(2) CRF discontinuation visits will be mapped to the earliest missing analysis visit based on the relative day of assessment as follows:

Assessments and tests	Relative Day	Analysis Visit
PANSS, CGI-S, DIEPSS, C-SSRS, Skin irritation assessment, Body weight, Vital signs	Day 1 to 11	Week 1, 2, 4, 6
	Day 12 to 25	Week 2, 4, 6
	Day 26 to 39	Week 4, 6
	Day 40 or later	Week 6
12-lead ECG, Pharmacokinetic	Day 1 to 11	Week 1, 2, 6
	Day 12 to 25	Week 2, 6
	Day 26 or later	Week 6
Laboratory test	Day 1 to 25	Week 2, 6
	Day 26 or later	Week 6

Note: non-missing analysis visits will not be replaced.

(3) CRF unscheduled visits will be mapped to the earliest missing analysis visit based on the relative day of assessment as follows:

Assessment and tests	Relative Day	Analysis Visit
PANSS, CGI-S, DIEPSS, C-SSRS, Skin irritation assessment, Body weight, Vital signs	Day 1 to 11	Week 1
	Day 12 to 25	Week 2
	Day 26 to 39	Week 4
	Day 40 or later	Week 6
12-lead ECG, Pharmacokinetic	Day 1 to 11	Week 1
	Day 12 to 25	Week 2
	Day 26 or later	Week 6
Laboratory test	Day 1 to 25	Week 2
	Day 26 or later	Week 6

If more than one unscheduled visits satisfy the condition, the earliest one

will be mapped to the analysis visit

Note: non-missing analysis visits will not be replaced.

B. DSP-5423P treatment period

(i) On-Treatment Baseline analysis visit

(1) 40 and 80 mg group in the double-blind treatment phase

Same as the Baseline analysis visit for the double-blind treatment phase.

(2) Placebo group in the double-blind treatment phase

Defined as the last non-missing data in the double-blind treatment phase including unscheduled visits assessed on or before the On-treatment Day 1.

(ii) Post-baseline data

(1) 40 and 80 mg group in the double-blind treatment phase

Defined as the non-missing data on 'On-treatment Day 1' through 7 days after the final application of DSP-5423P, except for Screening and Day 1 (Baseline) visit.

(2) Placebo group in the double-blind treatment phase

Defined as the non-missing data on a day after 'On-treatment Day 1' through 7 days after the final application of DSP-5423P.

(iii) Post-baseline analysis visit for the 40 and 80 mg group

The post-baseline data will be mapped to post-baseline analysis visits, ie, On-treatment Week 1, 2, 4, 6, 7, 8, 10, 14, 18, 22, 26, 30, 34, 42, 50, and 58 according to the CRF visits as follows. Unscheduled visits of the open-label treatment phase will not be mapped.

(1) Scheduled visits except for the discontinuation visits will be mapped regardless of the actual day of assessment as follows:

CRF Visits	DB W1	DB W2	DB W4	DB W6
Analysis Visits	OnT W1	OnT W2	OnT W4	OnT W6
CRF Visits	OL W1	OL W2	OL W4	OL W8
Analysis Visits	OnT W7	OnT W8	OnT W10	OnT W14
CRF Visits	OL W12	OL W16	OL W20	OL W24
Analysis Visits	OnT W18	OnT W22	OnT W26	OnT W30
CRF Visits	OL W28	OL W36	OL W44	OL W52
Analysis Visits	OnT W34	OnT W42	OnT W50	OnT W58

DB, double-blind; OL, open-label; OnT, on treatment; W, Week

(2) Discontinuation visits will be mapped to the earliest missing analysis visit based on the relative day of assessment as follows:

✧ PANSS, CGI-S, DIEPSS, C-SSRS, Skin irritation assessment, Body weight, Vital signs

Relative Day	Analysis Visit
Day 1 to 11	OnT W1, 2, 4, 6
Day 12 to 25	OnT W2, 4, 6
Day 26 to 39	OnT W4, 6
Day 40 or later	OnT W6
OL Day 1 to 11	OnT W7, 8, 10, 14, 18, 22, 26, 30, 34, 42, 50, or 58
OL Day 12 to 25	OnT W8, 10, 14, 18, 22, 26, 30, 34, 42, 50, or 58
OL Day 26 to 49	OnT W10, 14, 18, 22, 26, 30, 34, 42, 50, or 58
OL Day 50 to 77	OnT W14, 18, 22, 26, 30, 34, 42, 50, or 58
OL Day 78 to 105	OnT W18, 22, 26, 30, 34, 42, 50, or 58
OL Day 106 to 133	OnT W22, 26, 30, 34, 42, 50, or 58
OL Day 134 to 161	OnT W26, 30, 34, 42, 50, or 58
OL Day 162 to 189	OnT W30, 34, 42, 50, or 58
OL Day 190 to 238	OnT W34, 42, 50, or 58
OL Day 239 to 294	OnT W42, 50, or 58
OL Day 295 to 350	OnT W50 or 58
OL Day 351 or later	OnT W58

Note: non-missing analysis visits will not be replaced.

✧ 12-lead ECG, Pharmacokinetic

Relative Day	Analysis Visit
Day 1 to 11	OnT W1, 2, 6
Day 12 to 25	OnT W2, 6
Day 26 or later	OnT W6
OL Day 1 to 49	OnT W10, 18, 26, 34, 42, 50, or 58
OL Day 50 to 105	OnT W18, 26, 34, 42, 50, or 58
OL Day 106 to 161	OnT W26, 34, 42, 50, or 58
OL Day 162 to 238	OnT W34, 42, 50, or 58
OL Day 239 to 294	OnT W42, 50, or 58
OL Day 295 to 350	OnT W50 or 58
OL Day 351 or later	OnT W58

Note: non-missing analysis visits will not be replaced.

✧ Laboratory test

Relative Day	Analysis Visit
Day 1 to 25	OnT W2, 6
Day 26 or later	OnT W6
OL Day 1 to 49	OnT W10, 18, 26, 34, 42, 50, or 58
OL Day 50 to 105	OnT W18, 26, 34, 42, 50, or 58
OL Day 106 to 161	OnT W26, 34, 42, 50, or 58

OL Day 162 to 238	OnT W34, 42, 50, or 58
OL Day 239 to 294	OnT W42, 50, or 58
OL Day 295 to 350	OnT W50 or 58
OL Day 351 or later	OnT W58

Note: non-missing analysis visits will not be replaced.

(3) CRF unscheduled visits in the double-blind phase will be mapped to the earliest missing analysis visit based on the relative day of assessment as follows:

Relative Day	Relative Day	Analysis Visit
PANSS, CGI-S, DIEPSS, C-SSRS, Skin irritation assessment, Body weight, Vital signs	Day 1 to 11	OnT W1
	Day 12 to 25	OnT W2
	Day 26 to 39	OnT W4
	Day 40 or later	OnT W6
12-lead ECG, Pharmacokinetic	Day 1 to 11	OnT W1
	Day 12 to 25	OnT W2
	Day 26 or later	OnT W6
Laboratory test	Day 1 to 25	OnT W2
	Day 26 or later	OnT W6

If more than one unscheduled visits satisfy the condition, the earliest one will be mapped to the analysis visit.

Note: non-missing analysis visits will not be replaced in this step.

(iv) Post-baseline analysis visit for the placebo group

The post-baseline data will be mapped to post-baseline analysis visits, ie, On Treatment Week 1, 2, 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52 according to the CRF visits as follows. Unscheduled visits of the open-label treatment phase will not be mapped.

(1) Scheduled visits except for the discontinuation visits will be mapped regardless of the actual day of assessment as follows:

CRF Visits	OL W1	OL W2	OL W4	OL W8
Analysis Visits	OnT W1	OnT W2	OnT W4	OnT W8
CRF Visits	OL W12	OL W16	OL W20	OL W24
Analysis Visits	OnT W12	OnT W16	OnT W20	OnT W24
CRF Visits	OL W28	OL W36	OL W44	OL W52
Analysis Visits	OnT W28	OnT W36	OnT W44	OnT W52

OL, open-label; OnT, on treatment; W, Week

(2) Discontinuation visits will be mapped to the earliest missing analysis visit based on the relative day of assessment as follows:

✧ PANSS, CGI-S, DIEPSS, C-SSRS, Skin irritation assessment, Body weight, Vital signs

Relative Day	Analysis Visit
OL Day 1 to 11	OnT W1, 2, 4, 8, 12, 16, 20, 24, 28, 36, 44, or 52
OL Day 12 to 25	OnT W2, 4, 8, 12, 16, 20, 24, 28, 36, 44, or 52
OL Day 26 to 49	OnT W4, 8, 12, 16, 20, 24, 28, 36, 44, or 52
OL Day 50 to 77	OnT W8, 12, 16, 20, 24, 28, 36, 44, or 52
OL Day 78 to 105	OnT W12, 16, 20, 24, 28, 36, 44, or 52
OL Day 106 to 133	OnT W16, 20, 24, 28, 36, 44, or 52
OL Day 134 to 161	OnT W20, 24, 28, 36, 44, or 52
OL Day 162 to 189	OnT W24, 28, 36, 44, or 52
OL Day 190 to 238	OnT W28, 36, 44, or 52
OL Day 239 to 294	OnT W36, 44, or 52
OL Day 295 to 350	OnT W44 or 52
OL Day 351 or later	OnT W52

Note: non-missing analysis visits will not be replaced.

✧ 12-lead ECG, Laboratory test, Pharmacokinetic

Relative Day	Analysis Visit
OL Day 1 to 49	OnT W4, 12, 20, 28, 36, 44, or 52
OL Day 50 to 105	OnT W12, 20, 28, 36, 44, or 52
OL Day 106 to 161	OnT W 20, 28 36, 44, or 52
OL Day 162 to 238	OnT W28, 36, 44, or 52
OL Day 239 to 294	OnT W36, 44, or 52
OL Day 295 to 350	OnT W44, or 52
OL Day 351 or later	OnT W52

Note: non-missing analysis visits will not be replaced.

C. Open-label treatment phase

For the analysis of open-label treatment phase, analysis visits for all treatment groups are derived using the same algorithm for the placebo group for the DSP-5423P treatment period.

6.4 Missing Data

Individual missing item in any scale will not be imputed. For the rating scales that consist of more than one item, if any item is missing, then the total and subscale scores will also be handled as missing. For example, if one item of PANSS positive subscale is missing, then the PANSS total score, the PANSS subscale scores, and the PANSS five-factor model scores will be missing.

In computing LOCF, unscheduled visits in the double-blind treatment phase will be used. For example, for the double-blind treatment phase, Week 6 (LOCF) endpoint will be the last observation of the post-baseline data specified in 6.3 A. Unscheduled visits in the open-label treatment phase will not be used for Week 52 (LOCF) endpoint.

In the efficacy analysis on data collected in the double-blind treatment phase, the primary method for handling of missing data will be the MMRM without explicit imputations for missing data. The LOCF method will be used with analysis of covariance (ANCOVA) as additional sensitivity analysis. The final post-baseline data in the double-blind treatment phase (on or after Day 1 and through 7 days after the date of final application of the study drug for the double-blind treatment phase) will be carried forward and will be defined as the Week 6 (LOCF) endpoint.

6.5 Partial Dates

6.5.1 Adverse Events

End date will be imputed first. Start date imputed based on imputed end date. If year of the date is missing, the date will be imputed according to the following rules.

End date:

1) If ongoing is checked, no imputation will be performed.
2) If ongoing is not checked and end date is totally missing, then end date will be imputed as date of the last visit.
3) If only day of end date is missing, end date will be imputed as the earlier one of following dates: the last day of that month and date of the last visit.
4) If only month (or both month and day) of end date is missing, end date will be imputed as the earlier one of following dates: the last day (Dec31) in that year and date of the last visit.

Start date:

1) If start date is totally missing and end date is also missing (ongoing), no imputation will be performed.
2) If start date is totally missing and end date is not missing, start date will be imputed as the earlier one of following dates: end date of AE and date of the first dose of study medication.

3) If only day of start date is missing, and start date is in the same month of first study medication, start date will be imputed as earlier one of following non-missing dates: end date of AE and date of the first dose of study medication.
4) If only day of start date is missing, and start date is not in the same month of first study medication, start date will be imputed as the first day in that month.
5) If only month (or both month and day) of start date is missing, and start date is in the same year of first study medication, start date will be imputed as earlier one of following non-missing dates: end date of AE and date of first dose of study medication.
6) If only month (or both month and day) of start date is missing, and start date is not in the same year of first study medication, start date will be imputed as the first day (Jan01) in that year.

6.5.2 Prior/Concomitant Medication

If year of the date is missing, the date will be imputed according to the following rules.

End date:

1) If ongoing is checked, no imputation will be performed.
2) If ongoing is not checked and end date is totally missing, then end date will be imputed as date of the last visit.
3) If only day of end date is missing, end date will be imputed as the earlier one of following dates: the last day of that month and date of the last visit.
4) If only month (or both month and day) of end date is missing, end date will be imputed as the earlier one of following dates: the last day (Dec31) in that year and date of the last visit.

Start date:

1) If start date is totally missing, no imputation will be performed. If the medication is 'started prior to study' (checked in the CRF), then the medication is set to be a prior medication. Otherwise, the mediation is neither prior nor concomitant.
2) If only day of start date is missing, start date will be imputed as the first day in that month.
3) If only month (or both month and day) of start date is missing, start date will be imputed as the first day (Jan01) in that year.

6.5.3 First/Current Episode of Schizophrenia

For the purpose of the estimation of disease duration, the day of onset date of first/current episode will be imputed as the first day in that month.

1) If onset date is totally missing, no imputation will be performed.
2) If only month of onset date is missing, and onset date is not in the same year of informed consent, onset date will be imputed as June 30th.
3) If only month of onset date is missing, and onset date is in the same year of informed consent, onset date will be imputed as previous day of informed consent.

6.6 Pooled Center

Some centers may have less than 10 subjects, and these will be pooled. The pooling system works as follows: For each country, rank the centers by ascending order by site ID, combine the centers to ensure there are at least 20-30 subjects in each pooled center. Pooled centers will be determined before unblinding, and the list of pooled centers will be attached in the SAP (Appendix II).

6.7 Antipsychotics, antiparkinson drugs, psychotropic drugs, and hypnotic drugs

Classification of prior and concomitant drugs will be based on the category chosen in Prior and Concomitant Medications CRF forms.

6.8 Rating Scales

6.8.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS is an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The patient is rated from 1 to 7 on 30 different items across three subscales. A score of 1 indicates absence of symptoms absent while 7 indicates extreme symptoms.

The PANSS total score will be calculated as the score sum of all 30 items, and it ranges from 30 (least severe) to 210 (most severe).

The PANSS positive subscale is defined as the score sum of all 7 items within this subscale. The possible values are 7 (least severe) to 49 (most severe). The 7 items are delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility

The PANSS negative subscale is defined as the score sum of all 7 items within this subscale. The possible values are 7 (least severe) to 49 (most severe). The 7 items are blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking

The PANSS general psychopathology subscale is defined as the score sum of 16 items within this subscale. The possible values range from 16 (least severe) to 112 (most severe). The 16 items are somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance

Additionally, the PANSS five-factor model will also be considered, which is based on the sum of the following items:

Negative symptoms: Blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, and active social avoidance
Excitement: Excitement, hostility, tension, and poor impulse control
Cognitive disorders: Conceptual disorganization, difficulty in abstract thinking, mannerisms and posturing, disorientation, and poor attention
Positive symptoms: Delusions, grandiosity, suspiciousness/feelings of persecution, and unusual thought content
Anxiety/depression: Hypochondria, anxiety, feelings of guilt, depression, and Preoccupation

6.8.2 Clinical Global Impression – Severity of Illness (CGI-S)

The CGI-S is a research rating tool of the subject's current disease state on a 7-point scale of 1 to 7. A value of 0 represents "Not assessed", and the remaining values 1-7 represent "Normal, not at all ill" (1) through to "Among the most extremely ill subjects" (7). Any "Not assessed" items will be treated as missing and not left as zero in analysis datasets.

6.8.3 Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS)

The DIEPSS is a rating tool of extrapyramidal symptoms induced by antipsychotics and consist of 8 individual items and one global assessment; overall severity. The severity of each item is on a 5-point scale of 0 to 4. A value of 0 represents "None, Normal", and the remaining values 1-4 represent "Minimal, Questionable" (1) through to "severe" (4). The items covered include gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, dyskinesia and overall severity. DIEPSS total score is defined as the sum of 8 item scores not including overall severity.

6.8.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a rating tool designed to systematically assess and track suicidal behavior and ideation throughout the study. The C-SSRS is divided into four sections: "Suicide Ideation", "Intensity of Ideation", "Suicidal behavior" and "Actual attempts". "Suicide Ideation" and "Suicidal behavior" consist questions that require a "Yes" or "No" response with options to enter free text. "Intensity of Ideation" questions range from (1) (least severe) to (5) (most severe) with the exception of reasons for ideation question which ranges from (0) (Does not apply) to (5) "Completely to end the pain". For "Actual attempts" category, this is split into actual lethality (ranges from 0 [No damage] to 5, [Death]) and potential lethality (ranges from 0 [Not likely to cause injury] to 2 [behavior likely to result in death despite available medical care]).

7 STATISTICAL METHODS

7.1 General Principles

All data processing, summarization and analyses will be performed using the SAS enterprise 5.1 (SAS 9.3) or higher on SAS hosted environment, unless otherwise specified.

Unless otherwise specified, data will be displayed using the following treatment group labels, in the order presented:

1) Double-blind treatment phase

- Placebo group is labelled as PLCB
- DSP-5423P 40 mg group is labelled as 40MG
- DSP-5423P 80 mg group is labelled as 80MG
- Combined group of DSP-5423P 40 mg and 80 mg group is labelled as Active
- Combined group of DSP-5423P 40 mg, 80 mg and placebo group is labeled as

Overall

Treatment groups for tables and figures

	PLCB	40MG	80MG	Active	Overall
Efficacy	Y	Y	Y		
Safety	Y	Y	Y	Y	
PK		Y	Y		
Others *	Y	Y	Y	Y	Y

* subject disposition, analysis populations, demographics, psychiatric history, prior and concomitant medications, treatment compliance, treatment exposure. Active group will not be displayed for efficacy analyses.

2) Open-label treatment phase and DSP-5423P treatment period

For tables and figures for the open-label treatment phase and DSP-5423P treatment period, subjects are summarized based on the treatment group in the double-blind treatment phase as, PLCB-to-FLEX DOSE, 40MG-to-FLEX-DOSE, 80MG-to-FLEX DSOE, Active-to-FLEX DOSE, and Overall-to-FLEX DOSE. PK analysis for the open-label treatment phase will be based on the latest dose before the PK sampling.

All data collected will be presented in listings by treatment group, subject, visit and date, unless otherwise specified.

Data will be presented in summary tables by treatment group, assessment and visit (where applicable).

Continuous parameters will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max) values. Mean and median will be displayed to one more decimal place than the original value; min and max will keep the same number of decimal places. SD will be displayed to two more decimal places from the original value. For the case of CGI-S, another decimal point will be added to mean, median, and SD following the rules above. With regard to Pharmacokinetics parameters, Geometric Mean will be displayed to one more decimal place than the original value, and CV% and Geometric CV% will be done to one decimal place. M1/blonanserin will be displayed to three decimal place.

Categorical parameters will be summarized by presenting the number and percentage of subjects in each category. All percentages will be reported to one decimal place, unless otherwise specified.

In any appropriate analyses, estimates of Least square means (LS Means) and LS Means for the treatment difference will be displayed to one more decimal place than the original value; its SE and 95% CI will be displayed to two more decimal place than the original value or one more decimal place than the original value, respectively. Note that only for the case of analysis of CGI-S, one more decimal will be add on for the parameters above.

Odds Ratio and its 95% CI will be displayed to two decimal places.

Dates will be displayed as YYYY-MM-DD.

All statistical inference will be performed with two-sided tests at the significance level of 0.05 whenever appropriate. All confidence intervals (CIs) will be two-sided with 95% coverage, unless otherwise specified.

All p-values will be rounded to three decimal places; p-values less than 0.001 will be presented as '< 0.001' and p-values greater than 0.999 will be presented as '>0.999' in all tables. Same logic will be applied to adjusted p-value to be obtained in the efficacy primary analysis.

7.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by treatment group and overall, and will include the number and percentage of subjects for the double-blind treatment phase and the open-label treatment phase, the denominator of the percentage will be the number of randomized subjects and the number of the open-label population, respectively. Summaries of subject disposition will be repeated by country for both treatment phases.

For the double-blind treatment phase, the following information will be reported:

- informed consent obtained,
- not enrolled in the wash-out phase; with breakdown by reason for disposition,
- enrolled in the wash-out phase,
- not randomized; with breakdown by reason for disposition,
- randomized,

- not treated in the double-blind treatment phase; with breakdown by reason for disposition,
- treated in the double-blind treatment phase,
- completed the double-blind treatment phase,
- discontinued from the double-blind treatment phase; with breakdown by reason for disposition.

For the open-label treatment phase, the following information will be reported:

- completed the double-blind treatment phase,
- not treated in the open-label treatment phase; with breakdown by reason for disposition,
- treated in the open-label treatment phase,
- Ongoing; displayed ONLY for interim data analysis,
- completed the open-label treatment phase,
- discontinued from the open-label treatment phase; with breakdown by reason for disposition.

The number and percentage of subjects who included in each analysis population will be summarized for the double-blind treatment phase and the open-label treatment phase, where the denominator of the percentage will be the number of randomized subjects and the number of subject treated at least once in the open-label treatment phase, respectively. These summaries will be repeated by country.

For the double-blind treatment phase, the following analysis populations are of interest:

- mITT population,
- PP population,
- Safety population,
- PK population.

For the open-label treatment phase, the following analysis populations are of interest:

- Open-label population,
- DSP-5423P dosed population,
- PK population.

7.3 Important Protocol Deviations

All-important protocol deviations (IPDs), including those leading to exclusion from the PP population will be listed and summarized by treatment group and overall for the randomized subjects. Tables will be further breakdown by country. IPDs for the double-blind treatment phase will be identified at a blind data review meeting before unblinding. IPDs for the open-label treatment phase will also be identified before the data analysis of open-label treatment phase.

Subjects with any deviation of inclusion or exclusion criteria will be listed respectively.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for the mITT, PP, safety, open-label, PK only for the double-blind treatment phase, and DSP-5423P dosed populations. Summaries will be repeated by race and country for the mITT, safety, and DSP-5423P dosed population.

Standard descriptive statistics will be presented for the following continuous variables:

- Age (years) [Use SDTM variable, AGE.DM]
- Baseline weight (kg);
- Height (cm);
- Baseline body mass index (kg/m^2) [calculated as ($weight/height^2$) where weight is in kg and height is in m, reported to one decimal place];
- Baseline PANSS total score,
- Baseline CGI-S score,
- Baseline DIEPSS total score

The number and percentage of subjects will be presented for the following categorical variables:

- Sex: Female; Male,
- Age (years): <65; ≥65,
- Race: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other,
- Ethnicity: Hispanic or Latino; Not Hispanic or Latino,
- Country,
- Hospitalization status on the day of informed consent: Inpatient; Outpatient
  For Inpatient, within 3 months (90 days); over 3 months; unknown
- Concomitant diseases: Yes; No,
- Baseline CGI-S score; 1; 2; 3; 4; 5; 6; 7,

No formal tests of statistical significance will be performed on the demographic and baseline.

Other baseline measurements, such as laboratory assessments, vital signs and ECG, will be summarized by treatment group and overall with the post-baseline measurements in separate tables respectively.

7.4.1 Psychiatric History

History of schizophrenia will be listed and summarized by treatment group and overall for the mITT, PP, safety, open-label, PK only for the double-blind treatment phase, and DSP-5423P dosed populations. Summaries will be repeated by country for the mITT, safety, and DSP-5423P dosed population.

Standard descriptive statistics will be presented for the continuous variables:

- Number of episode of schizophrenia,
- Age at the first onset of schizophrenia,
- Duration of illness; years since onset of the first episode [calculated as (informed consent date – date of onset date of the first episode) / 365.25 and reported as year with one decimal place],

- Duration of current episode; months since onset of the current episode [calculated as (informed consent date – date of onset date of the current episode) /30.4375 and reported as month with one decimal place],

The number and percentage of subjects will be presented for the following categorical variables:

- Number of episodes of schizophrenia; 1; 2; 3; 4; 5 or more; Unknown,
- Age at initial onset of schizophrenia;
  19 or less; 20 to 29; 30 to 39; 40 to 49; 50 or more
- Duration of illness;
  <1; >=1 to <5; >=5 to <10; >=10 to <20; >=20 to <30; >=30; Unknown
- PANSS composite subscale at baseline:
  Positive subscale score > Negative subscale score;
  Positive subscale score = Negative subscale score;
  Positive subscale score < Negative subscale score
- Baseline PANSS total score: <100, >=100 to <120, >=120

7.4.2 Medical History

Medical condition/event will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 19.1]. All medical condition/event will be listed, and number and percentage of subjects with any medical condition/event will be summarized for the safety population and DSP-5423P dosed population by system organ class (SOC), preferred term (PT), and treatment group.

7.4.3 Prior and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by Covance using the WHO Drug Dictionary [March 1, 2014 version], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are defined as those taken prior to initial dose of study medication, ie, those medications with a start date before the date of initial application of study medication in the double-blind treatment phase.

Concomitant medications are defined as those taken during the double-blind treatment phase and the DSP-5423P treatment period as described below. Note that the concomitant and prior medications definitions are not mutually exclusive, ie, a medication can be classified as both prior and concomitant.

For the double-blind treatment phase, concomitant medications are those with a start date on or after the initial application date of double-blind treatment phase and up to the final application date of double-blind treatment phase, or those with both a start date before the initial application date of double-blind treatment phase and an end date on or after the initial application date of double-blind treatment phase.

For the DSP-5423P treatment period, concomitant medications are those with a start date on or after the first date of DSP-5423P treatment but before the final application date of DSP-5423P treatment, and those with both a start date before the initial application date of DSP-5423P treatment and an end date on or after the initial application date of DSP-5423P treatment.

If a start date of medication is missing after applying imputation rules, the corresponding medication will be classified as concomitant medication. Note that this is only applicable if the initial application date of study medication is not missing.

Prior medications and concomitant medications will be listed and summarized for the double-blind treatment phase on mITT population and the safety population by treatment group, and for the DSP-5423P treatment period on the DSP-5423P dosed population. Tables are repeated by country. The number and percentage of subjects taking medication will be summarized by pharmacological subgroup (ATC-Level 3) and preferred names. Also number and percentage of subjects taking any antipsychotics, antiparkinson drugs, psychotropic drugs, or hypnotic drugs will be summarized as well. These categories will be based on ones captured in CRF. Note that listing for concomitant medications in double-blind treatment phase will include medications taken after the final application date of double-blind treatment phase, as well as concomitant medications. Also listing for concomitant medications in DSP-5423P treatment period will include medications taken after the final application date of DSP-5423P treatment, as well as concomitant medications.

The number and percentage of subjects with concomitant use of antiparkinson drugs in the double-blind treatment phase by treatment group, and in the DSP-5423P treatment period will be summarized. The number and percentage of subjects with concomitant use of antiparkinson drugs in the DSP-5423P treatment period will be additionally summarized by treatment duration: Day -1, Week 1 to 2, Week 3 to 4, Week 5 to 6, Week 7 to 12, Week 13 to 24, Week 25 to 36, Week 37 or later, Overall

* Week 1=Day 1 to 7, Week 2=Day 8 to 14

7.5 Measurements of Treatment Compliance

The level of treatment compliance will be calculated, listed and summarized by treatment group for the mITT population and the safety population for the double-blind treatment phase, the DSP-5423P treatment population for DSP-5423P dosed period and for the open-label population for the open-label treatment phase. Summaries will be repeated by country.

Double-blind treatment phase

- Compliance (percentage) = (actual number of patches applied/ expected number of patches should have been applied) *100.
- Expected number of patches = 2*(the final application date of study medication in the double-blind treatment phase – the initial application date of study medication in the double-blind treatment phase +1) = 2*treatment duration (days).

Open-label treatment phase

- Compliance (percentage) = (actual number of patches applied/ expected number of patches should have been applied) *100.
- Expected number of patches = sum of (number of prescribed patches per day *(start date of each prescription period – end date of each prescription period +1)). Numbers of 'daily' prescribed patches are 1, 2, and 2 for 40, 60, and 80 mg/day, respectively.

  In case of prescription periods are not continuous, ie, there are periods for which no patches are prescribed, these periods are not taken account into calculation.

If any information to calculate the compliance is missing for a subject, then the compliance for the subject is set as missing.

Compliance is considered to have been achieved if the treatment compliance is between 80% and 120%, inclusive. In addition, the following percentage compliance categories will also be presented:

- <80%
- 80 to 120%
- >120%

7.5.1 Extent of Treatment Exposure

Duration of treatment exposure will be calculated and summarized by treatment group for the double-blind treatment phase on the mITT population and the safety population, for the open-label treatment phase on the open-label population, and for the DSP-5423P treatment period on the DSP-5423P dosed population. For the open-label treatment phase and DSP-5423P treatment period, mean daily dose, modal daily dose, last daily dose, Maximum dose, and Cumulative dose will also be presented. Summaries will be repeated by country.

Duration of exposure

Duration of exposure will be calculated for the double-blind treatment phase, open-label treatment phase, and the DSP-5423P treatment period:

- Duration of exposure will be defined in days as the final application date – the initial application date + 1. If either the date is missing, then the duration of exposure will be missing.
- For each treatment phase which is the double-blind treatment phase, open-label treatment phase, or the DSP-5423P treatment period, the initial and final application date corresponding to each phase will be utilized for derivation of duration of exposure. Note that for the DSP-5423P treatment period, and subjects who take placebo in the double-blind treatment phase, initial application date will be a one that DSP-5423P is initially applied.

- Duration of exposures will be summarized in summary statistics as well as the number and percentage of subjects for the following categories.
    - The double-blind treatment phase: 1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 28 days, 29 to 35 days, 36 days or more
    - The open-label treatment phase: Week 1 to 6*, 7 to 12, 13 to 24, 25 to 36, 37 to 48, 49 or later
    - The DSP-5423P treatment period: Week 1 to 6*, 7 to 12, 13 to 24, 25 to 36, 37 to 48, 49 or later

      *Week 1=Day 1 to 7, Week 2=Day 8 to 14

Mean daily dose

Mean daily dose will be calculated and summarized in summary statistics only for the open-label treatment phase and DSP-5423P treatment period:

- Mean daily dose (mg/day) = total dose of prescribed patches (mg)/duration of exposure (day).
- Total dose of prescribed patches = sum of (total dose of prescribed patches for the prescription period * (start date of the prescription period – end date of the prescription period +1)).

Modal daily dose

Modal daily dose will be calculated only for the open-label treatment phase and DSP-5423P treatment period:

- Modal daily dose is the most frequently prescribed daily dose during the treatment phase. In the case where there is more than one most frequent dose, eg, both 40 and 60 mg/day are equally frequent then the maximum dose level (eg, 60 mg/day) will be the modal daily dose.
- Modal daily dose will be presented as the number and percentage of subjects for the following categories: 40 mg, 60 mg, 80 mg and Missing

Last daily dose

Last daily dose will be calculated and summarized in summary statistics only for the open-label treatment phase and DSP-5423P treatment period:

- Last daily dose is the prescribed daily dose at the final prescription for the subject during the treatment phase.
- Last daily dose will be presented as the number and percentage of subjects for the following categories: 40 mg, 60 mg, 80 mg and Missing

Maximum dose

Maximum dose will be presented only for the open-label treatment phase and DSP-5423P treatment period:

- Maximum dose is the prescribed daily dose throughout the treatment phase.
- Maximum dose will be presented as the number and percentage of subjects for the following categories: 40 mg, 60 mg, 80 mg and Missing

Cumulative dose

Cumulative dose will be calculated and summarized in summary statistics only for the open-label treatment phase and DSP-5423P treatment period:

- Cumulative dose is Sum of prescribed daily dose x duration of each prescription (days)

7.6 Efficacy

Efficacy data will be listed.

7.6.1 Primary Efficacy Analysis

The primary efficacy variable is the mean change in PANSS total score from baseline at Week 6 for testing the superiority of DSP-5423P (40 or 80 mg/day) to placebo in the double-blind treatment phase.

Hypothesis:

Let μ_{40}, μ_{80}, and $\mu_{placebo}$ represent the mean changes in PANSS total score from baseline at Week 6 in the DSP-5423P 40 mg group, DSP-5423P 80 mg group, and placebo group, respectively. The following two hypotheses will be tested to compare the mean changes at Week 6 of each DSP-5423P group with that of the placebo group:

- H_{01}: $\mu_{40}=\mu_{placebo}$ versus the alternate H_{11}: $\mu_{40} \neq \mu_{placebo}$.
- H_{02}: $\mu_{80}=\mu_{placebo}$ versus the alternate H_{12}: $\mu_{80} \neq \mu_{placebo}$.

A mixed model for repeated measurements (MMRM) method will be utilized for the mITT population. The MMRM model will include treatment as a categorical factor, visit (Week 1, 2, 4, and 6; as a categorical factor), pooled study center, baseline PANSS total score as a covariate, and the treatment-by-visit interaction as fixed effects with repeated visits. An unstructured covariance matrix will be used for the within-subject correlation and the Kenward-Rogers approximation will be used to calculate the denominator degree of freedom. In the case of a convergence problem with the unstructured covariance matrix, the following structures with a robust sandwich estimator for the standard error of the fixed effect estimates will be assessed in a sequential fashion: heterogeneous Toeplitz, heterogeneous first-order autoregressive, and Toeplitz. Of the three covariance structures, the first structure yielding convergence will be used for the MMRM analysis. P-values for comparisons of the primary efficacy variable at Week 6 between DSP-5423P groups and the placebo group will be adjusted using the Hochberg procedure (4).

Effect sizes of 40 and 80 mg versus placebo at Week 6 will be calculated as the least square mean of treatment difference divided by square root of the variance estimate, ie, standard deviation (O'Kelly, 2014). Least square means estimates for the treatment difference between the active treatments and placebo treatment at Week 6 will be obtained using the MMRM model. To calculate the standard deviation of change from baseline at Week 6 based on MMRM model, the square root of the variance estimate for that visit, obtained from the SAS-estimated R matrix will be taken (O'Kelly & Ratitch, 2014). The variance estimates for the visits are obtained differently dependent upon the covariance structure being applied for the model. If the MMRM converges using the planned unstructured covariance structure, then the diagonal of the R matrix will be used for variance estimate at each visit. In the case of non-convergence and the use of a heterogeneous Toeplitz based MMRM or first order auto-regressive MMRM then the diagonal cell corresponding to Week 6 from the R matrix can still be used to estimate the variance. However, in the case of non-convergence and the use of a regular Toeplitz based on MMRM, the diagonal from the first column of the R matrix can be used as the variance estimate.

This analysis will be repeated by country and race as well.

The mock SAS code for unstructured covariance model along with codes for the other backup models is provided below:

Initial model:

```
proc mixed data = &ads;
  class trt01p avisit site usubjid;
  model chg = trt01p avisit site base trt01p*avisit / DDFM=KR;
  repeated avisit /type=UN subject=usubjid r;
  lsmeans trt01p*avisit / diff cl alpha = 0.05;
  ods output diffs=diffs  ;
  ods output lsmeans = lsmeans;
  ods output r=r;
run;
```

In case of non-convergence of the initial model:

```
proc mixed data = &ads empirical
  class trt01p avisit site usubjid;
  model chg = trt01p avisit site base trt01p*avisit / DDFM=KR;
  repeated avisit /type=TOEPH subject=usubjid r;
  /* repeated avisit /type=ARH(1) subject=usubjid r;*/
  /* repeated avisit /type=TOEP   subject=usubjid r;*/
  lsmeans trt01p*avisit / diff cl alpha = 0.05;
  ods output diffs=diffs;
  ods output lsmeans = lsmeans;
  ods output r=r;
run;
```

For adjusted p-value:

```
data a;
  input Test$ Raw_P @@;
  datalines;
  test01 0.28282    test02 0.30688    test03 0.71022;

proc multtest inpvalues=a hoc;
run;
```

An analysis of sensitivity for the primary efficacy variable will be performed using an analysis of covariance (ANCOVA) model on the mITT population. The response variable for the model will be the change in PANSS total score from baseline at the LOCF endpoint. The ANCOVA model will include treatment as a categorical factor,

pooled study center, and baseline PANSS total score as a covariate. The MMRM and LOCF ANCOVA analysis will also be performed on the PP population to obtain additional information on the robustness of the results.

The mock SAS code for ANCOVA model is provided below:

```
proc mixed data = &ads;
  class trt01p site;
  model chg = trt01p site base;
  lsmeans trt01p / diff cl alpha = 0.05;
  ods output lsmeans = lsmeans;
run;
```

In addition to analysis described above, the PANSS total score and change from baseline will be summarized by visit (including LOCF endpoint) and treatment group. Summaries will be repeated for each PANSS item score in same manner, however Wilcoxon signed-rank test for change from baseline to LOCF endpoint within each treatment group will be conducted additionally.

The mock SAS code for Wilcoxon signed-rank test is provided below:

```
proc univariate data = &ads;
  by visitnum;
  where trt01p="XXX" ;
  var chg;
  output out=XX signrank = signrank;
run;
```

The estimates of the change from baseline in PANSS total score obtained by the primary analysis model will be plotted by treatment group and visit with +/-SE.

7.6.2 Secondary Efficacy Analysis

7.6.2.1.1 Double-blind treatment phase

1. Mean change in PANSS subscale scores from baseline at Week 6
2. Mean change in PANSS five-factor model scores from baseline at Week 6
3. Mean change in CGI-S score from baseline at Week 6

The secondary variables (1) to (3) will be analyzed using the MMRM method

described above for the primary efficacy variable in the mITT population. This analysis will be repeated by country. Also (3) will be repeated by race as well as country. The secondary variables (1) and (3) will also be analyzed using the LOCF ANCOVA on the mITT population by the method described above for the primary efficacy variable. Additionally, change from last measurement value in the double blind treatment phase for PANSS total score by visit will be summarized for the open-label population. This analysis will be repeated by country.
In addition to analysis described above, the secondary variables (1) to (3) and their change from baseline will be summarized by visit (including LOCF endpoint) and treatment group.

The estimates of the change from baseline in PANSS subscale scores, five factor model scores, and CGI-S score obtained by the MMRM model will be plotted with +/- SE.

Adjusted p-value will not be calculated in any secondary efficacy analysis, even though they use same MMRM method and options as the primary efficacy variable.

4. Proportion of subjects who achieve a response, defined as 20% or greater improvement from baseline in PANSS total score at Week 6

Subjects having a greater or equal to 20% improvement from baseline in PANSS total score at Week 6 (LOCF) will be defined as "responders". The PANSS total score percentage change will be defined as [(value at Week 6 (LOCF) – 30) – (baseline value – 30)] × 100 / (baseline value – 30). Subjects having a greater or equal to 30%, 40% and 50% improvement will also be analyzed.
The responder indicator will be set to 1 for responders, set to 0 for non-responder, or set to missing if the percentage is missing. A logistic regression will be performed utilizing the 0-1 responder indicator as the dependent variable, treatment and pooled study center as categorical variables and baseline PANSS total score as a covariate. If the model fails to converge, the model which replace pooled study center to country will be attempted. If still the model failed to converge, the model was attempted with only treatment group and baseline score. If the model ends up not to converge regardless of any attempts described earlier, that should be mentioned in the associated tables.
Estimates for odds ratio and its 95% CI and chi-square p-values will be presented for each DSP-5423P treatment group versus placebo. A similar summary will be presented by country. These analyses will be performed for the mITT population only.

The mock SAS code for logistic regression is given below:

```
proc logistic data-&ads;
class trt01p site / param=ref;
model responder(event='1')=trt01p site base;
contrast '40MG vs. PLCB' trt01p 1 0 / estimate=exp;
contrast '80MG vs. PLCB' trt01p 0 1 / estimate=exp;
ods output ContrastEstimate = ContrastEstimate;
run; * contrast statement need to be checked by the code list;
```

7.6.2.1.2 Time to Treatment Discontinuation

The time to treatment discontinuation for the double-blind treatment phase and the open-label treatment phase will be analyzed using the Kaplan-Meier method for m ITT population or the open-label population respectively. The time to treatment discontinuation will be listed.

- All cause discontinuation will be considered as an event in both the double-blind treatment phase and the open-label treatment phase.
- Subjects who completed the double-blind treatment phase, subjects will be censored at the final application date of the study medication of the double-blind treatment phase.
- Time to treatment discontinuation for the double-blind treatment phase will be determined as the final application date in the double-blind treatment phase – the initial application date in the double-blind treatment phase + 1.
- Subjects who completed the open-label treatment phase, subjects will be censored at the final application date of the study medication of the open-label treatment phase.
- Time to treatment discontinuation for the open-label treatment phase will be determined as the final application date in the open-label treatment phase – the initial application date in the open-label treatment phase + 1.

Kaplan-Meier estimate for 25, 50, and 75 percentiles for time to treatment discontinuation and Kaplan-Meier plots by treatment group will be provided. Additionally, in summary for the double-blind treatment phase, number and percentage of subjects who stay the study for 42 days and its 95%CI will be provided, and in summary for the open-label treatment phase, number and percentage of subjects who

stay the study up to 28 weeks (196 days), and 52 weeks (364 days) and its 95%CI will be provided,
These will be repeated by country. In this case, number and percentage of subjects who stay the study up to 52 weeks (364 days) and its 95%CI will be summarized only for Japan.

The mock SAS code for Kaplan-Meier analysis is given below:

```
proc lifetest data=&ads plots=survival(atrisk);
strata trt01p;
time tte*censor(1);
ods output quartiles=mst;
run;
* tte is the variable for time to discontinuation;
* if completer then censor=1; else censor=0;
```

7.6.2.1.3 DSP-5423P Treatment Period

1. Mean change in PANSS total score from the last evaluation before the initial application of DSP-5423P at each visit
2. Mean change in PANSS subscale scores from the last evaluation before the initial application of DSP-5423P at each visit
3. Mean change in PANSS five-factor model scores from the last evaluation before the initial application of DSP-5423P at each visit
4. Mean change in CGI-S score from the last evaluation before the initial application of DSP-5423P at each visit

Summary statistics for the variables (1) to (4) will be provided in tables and figures by visit and treatment group on the DSP-5423P dosed population. Only (1) and (4) will be repeated by country and race, however figures by race will not be needed.

The estimates of the change in the variables (1) to (4) obtained will be plotted by treatment group and visit with +/-SD

Summaries will be repeated for each PANSS item score in same manner, but Wilcoxon test for change from baseline to LOCF endpoint within each treatment group will be conducted additionally.

7.6.3 Sensitivity Analysis

This is described in the primary and secondary analyses section.

7.6.4 Subgroup Analysis

For the double-blind treatment phase:

Subgroup analysis will be performed for the mean change in PANSS total score and CGI-S score from baseline on the mITT population. The subgroup analysis will include sex, age, hospitalization status, antipsychotics use, and country. Age will be dichotomized as less than 65 years and older than or equal to 65 years. Subgroup analyses of before and after the interim analysis will also be performed where the before subgroup will consist of the subjects included in the interim analysis (1st to 251st randomized subjects) and the after subgroup consists of the remaining subjects. Antipsychotics use will be decided based on whether if subjects took any antipsychotics as prior medication or not. Antipsychotics will be identified up to Prior and Concomitant Medication category on CRF. Baseline characteristics and history of schizophrenia will also be summarized by before and after the interim analysis for the mITT and safety population.

For subgroup analyses by these variables other than country, inferential analysis of treatment-by-subgroup interaction at Week 6 will be performed for each subgroup variable using MMRM on the mITT population. The model will include fixed effects for treatment group, visit as a categorical variable, baseline score, pooled center, and treatment-by-visit treatment-by-subgroup, visit-by-subgroup, and treatment-by-subgroup-by-visit interactions. An unstructured covariance matrix will be used for the within-subject correlation and the Kenward-Rogers approximation will be used to calculate the denominator degree of freedom. In the case of a convergence problem with the unstructured covariance matrix, the following structures with a robust sandwich estimator for the standard error of the fixed effect estimates will be assessed in a sequential fashion: heterogeneous Toeplitz, heterogeneous first-order autoregressive, and Toeplitz.

Initial model:

```
proc mixed data = &ads;
  class trt01p avisit site usubjid subgroup;
  model chg = trt01p avisit site base subgroup trt01p*avisit
trt01p*subgroup subgroup*avisit trt01p*subgroup*avisit/ DDFM=KR;
  repeated avisit /type=UN subject=usubjid;
  lsmeans trt01p*subgroup*avisit / diff cl alpha = 0.05;
```

```
run;

In case of non-convergence of the initial model:
proc mixed data = &ads empirical
  class trt01p avisit site usubjid subgroup;
  model chg = trt01p avisit site base subgroup trt01p*avisit
trt01p*subgroup subgroup*avisit trt01p*subgroup*avisit/ DDFM=KR;
  repeated avisit /type=TOEPH subject=usubjid;
  /* repeated avisit /type=ARH(1) subject=usubjid;*/
  /* repeated avisit /type=TOEP   subject=usubjid;*/
  lsmeans trt01p*subgroup*avisit / diff cl alpha = 0.05;
run;
```

The subgroup analysis to be conducted by country or race will be performed using same MMRM model and options as the primary analysis detailed in 7.6.1., besides adjusted p-value, on the mITT population. The MMRM model will be applied by country or race respectively, not including subgroup factor like country or race into the mixed model as fixed factor.

In addition to analysis described above, PANSS total score and CGI-S and their change from baseline will be summarized by subgroup, visit (including LOCF endpoint), and treatment group for the mITT population.

DSP-5423P treatment period:

Subgroup analysis will be performed for the mean change in PANSS total score and CGI-S score from baseline. The subgroup analysis will include sex, age, hospitalization status, race, and country. PANSS total score and CGI-S score and their change from the on-treatment baselines will be summarized by subgroup, visit (including LOCF endpoint), and treatment group for the DSP-5423P dosed population.

7.7 Safety

Safety data will be listed.

7.7.1 Adverse Events

Treatment emergent AEs (TEAEs) are defined as follows:

- TEAEs (the double-blind treatment phase): Events with start date on or after the date of initial application of study drug in the double-blind treatment phase, and up to 17 days after the date of final application of study drug in the double-blind treatment phase and before the first application of DSP-5423P in the open-label treatment phase.
- TEAEs (DSP-5423P treatment period): Events with start date on or after the date of initial application of DSP-5423P either in the double-blind treatment period for 40MG and 80MG groups or in the open-label treatment period for placebo group and up to 17 days after the date of final application date of DSP-5423P.

AE with missing or incomplete start date after imputation will be considered as TEAE.

Treatment-related TEAE:
A treatment-related TEAE is defined as a TEAE for which the causal relationship to the study treatment is either 'definite', 'probable', or 'possible'.

Common TEAE:
Common TEAE in the double-blind treatment phase are PT of TEAEs experienced by 2% or more subjects in 40MG or 80MG group in the safety population.
Common TEAE in the DSP-5423P treatment period are PT of TEAEs experienced by 2% or more subjects in the overall-to-FLEX DOSE group in the DSP-5423P dosed population.

The summary of AEs will be limited to treatment-emergent AEs (TEAEs). The number and percentage of subjects with TEAEs during the double-blind treatment phase on the safety population and DSP-5423P treatment period on the DSP-5423P dosed population will be summarized by preferred term, system organ class, and treatment group. Summaries will be repeated by country and race.
Specifically, this will cover the following items:

- any TEAE;
- TEAE leading to death;
- TEAE leading to treatment discontinuation;
- serious TEAE;

- extrapyramidal TEAE;
- skin-related TEAE;
- treatment-related TEAE;
- treatment-related TEAE leading to death;
- treatment-related TEAE leading to treatment discontinuation;
- treatment-related serious TEAE;
- treatment-related extrapyramidal TEAE;
- treatment-related skin-related TEAE;

Skin-related TEAE is defined as the TEAE occurred at the application site (recoded in the CRF) and identified as TEAE with a wording "Application site" in MedDRA LLT.

The number and percentage of subjects reporting each TEAE will be summarized by system organ class (SOC) and preferred term (PT) for the double-blind treatment phase on the safety population and for the DSP-5423P treatment period on the DSP-5423P dosed population. Whenever appropriate, SOCs are sorted by alphabetically and PTs are sorted within SOC in descending order of frequency of the active group for the double-blind treatment phase and the Overall-to-FLEX DOSE group for the DSP-5423P treatment period. If there are ties, PTs are sorted by alphabetically. The following summaries will be produced for the double-blind treatment phase and DSP-5423P treatment period:

- TEAE by SOC and PT*;
- Common TEAE by PT#;
- treatment-related TEAE by SOC and PT;
- TEAE by maximum severity and PT;
    - This will be repeated for extrapyramidal TEAE and skin related TEAE
- TEAE leading to treatment discontinuation by SOC and PT+;
- Serious TEAE by SOC and PT;
- extrapyramidal TEAE by PT#+;
- skin related TEAE by PT#+;
- skin related TEAE by PT and application site;

- TEAEs by first onset (Day 1 to 7, Day 8 to 14, Day 15 to 28, Day 29 or later), SOC and PT in the double-blind treatment phase;
    - This will be repeated for extrapyramidal TEAE and skin related TEAE
- TEAEs by first onset (Week1 to 6, 1 to 13, 14 to 26, 27 to 39, 40 to 52, 53 or later, Week 1=Day 1 to 7, Week 2=Day 8 to 14), SOC and PT in the DSP-5423P treatment period;
    - This will be repeated for extrapyramidal TEAE and skin related TEAE
- TEAEs by DSP-5423P dose at onset (40MG, 60MG, 80MG), SOC and PT in the DSP-5423P treatment period;
- TEAEs by modal daily dose (40MG, 60MG, 80MG), SOC and PT in the DSP-5423P treatment period;
- TEAEs leading to dose reduced by SOC and PT in the DSP-5423P treatment period+;
- TEAEs leading to dose increased by SOC and PT in the DSP-5423P treatment period+;

  * Summaries will be repeated by country and race. # Summaries will be repeated by country. +: listing will be produced.

In the above summaries, unless otherwise specified, if a subject experienced more than one episode of a TEAE within a PT or a SOC, the subject is counted only once in the PT or the SOC.

For summaries based on DSP-5423P treatment period and on-going event carried from DB phase, the following items will be handled as described. No handling will be applied for items not listed below;

- Serious TEAE: if the event is flagged as serious at least one time throughout DSP-5423P treatment period, the event will be summarized as Serious TEAE.
- Causality: Causality will be prioritized as listed in order, "DEFINITE", "PROBABLE", "POSSIBLE" and "NOT RELATED" in on-going event.
- Severity: Severity will be prioritized as listed in order, "SEVERE", "MODERATE", "POSSIBLE" ,"MILD" in on-going event.

- Event leading to Dose Reduced: for on-going event, if the event is flagged as dose reduced in action taken at least one time throughout DSP-5423P treatment period, the event will be summarized as event concerned.
- Event leading to Dose Increased: for on-going event, if the event is flagged as dose increased in action taken, at least one time throughout DSP-5423P treatment period, the event will be summarized as event concerned.
- Application site: if on-going event have multiple application site throughout DSP-5423P treatment period, application site will not be prioritized, and the event will be counted per application site within associate PT.

For the summaries by maximum severity, if a subject experienced more than one episode of a TEAE within a PT, the subject is counted only once in the PT at the maximum severity. In determining maximum severity, severities are ranked from missing (not specified), mild, moderate, to severe. If the maximum severity is missing, the episode will be displayed as 'not specified'.

For the summaries of skin-related adverse events, if a subject experienced more than one episode of a TEAE within a PT for an application site of study drug, the subject is counted only once in the PT for the application site. If a subject had a PT occurred at different application sites, it will be counted per application site within associate PT.

For the summaries by first onset, if a subject experienced more than one episode of an TEAE within a PT, the subject is counted only once in the PT for the first episode. Denominator of percentage for each period of interest is the number of subjects who were treated with the study medication regardless of any suspensions of study medication between the initial and final date of application of study drug.

For the summaries by DSP-5423P dose at onset, if a subject experienced more than one episode of an TEAE within a PT, the subject is counted only once in the PT by DSP-5423P dose at onset. For example, if a subject has same PT twice but onset dose for each is not same, these PTs will appear one time each in different dose categories. Denominator of percentage for each dose is the number of subjects who have experienced the dose of interest at least once in the DSP-5423P treatment period in case that no DSP-5423P dose at onset is available, for example, the onset date is middle of prescribed periods or the onset date is after the final application, DSP-5423P dose at onset will be set to last non-missing dose taken at prior to the onset date.

No statistical comparisons of AEs between treatment groups will be performed.

Narrative of Serious AE will be produced by a subject who experienced SAE.

Hospitalization record will be listed.

7.7.2 DIEPSS

1. Mean change in DIEPSS total score (excluding overall severity) from baseline to Week 6
2. Mean change in individual DIEPSS scores from baseline to Week 6
3. Mean change in DIEPSS total score (excluding overall severity) from the last evaluation before the initial application of DSP-5423P at each visit
4. Mean change in individual DIEPSS scores from the last evaluation before the initial application of DSP-5423P at each visit

The variables (1) will be analyzed using MMRM and the LOCF ANCOVA methods described above for the primary efficacy variable for the safety population. Summary statistics for the safety variables (1), and (2), will be provided by visit including LOCF endpoint by treatment group for the safety population. (3) and (4) will be provided for DSP-5423P dosed population.

7.7.3 C-SSRS

The number and percentage of subjects with any suicidal ideation and behavior will also be summarized. In addition, the total number and percentage of subjects with each type of suicidal ideation (i.e. 'Wish to be Dead', 'Non-Specific Active Suicidal Thoughts', 'Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act', 'Active Suicidal Ideation with Some Intent to Act, without Specific Plan', and 'Active Suicidal Ideation with Specific Plan and Intent') and suicidal behavior (i.e. actual attempts, interrupted attempts, aborted attempts, and preparatory acts or behavior) will be presented at baseline and each post-baseline visit for the double-blind treatment phase and the DSP-5423P treatment period. Note that for the DSP-5423P treatment period summary, baseline in PLCB-to-FLEX DOSE will be taken from baseline in the double-blind treatment phase.

An overall summary based on all post-baseline visits will include the number and percentage of subjects who have each of the following, will be presented for the

double-blind treatment phase and the DSP-5423P treatment period.

- Maximum suicidal ideation after baseline,
- Any Suicidal Ideation after Baseline and no Suicidal Ideation after Baseline,
- Serious Suicidal Ideation after baseline,
- Suicidal behavior after baseline,
- Any Suicidal Behavior after Baseline and No Suicidal Behavior after Baseline,
- Suicidality after Baseline,
- Emergence of any suicidal ideation*: Subjects who had no suicidal ideation at Baseline and subsequently had any type of suicidal ideation during the treatment phase.
- Emergence of serious suicidal ideation*: Subjects who had no serious suicidal ideation (defined as score of 4 or 5 on the suicidal ideation severity rating**) at Baseline and subsequently had serious suicidal ideation during the treatment phase,
- Worsening of suicidal ideation: most severe suicidal ideation post-baseline was more severe than it was at baseline,
- Emergence of suicidal behavior*: Subjects who had no suicidal behavior at Baseline and subsequently had any type of suicidal behavior during the phase,
- Emergence of suicidality*: Subjects who had no suicidality (neither suicidal ideation nor suicidal behavior) at Baseline and subsequently had any type of suicidality (suicidal ideation or suicidal behavior) during the treatment phase.
- Any completed suicide: Subjects who completed suicide during the treatment phase.

* Subjects who have "Y" at baseline will be excluded from denominator in calculation of percentage.

** Regarding "Suicidal Ideation", in case that "Non-Specific Active Suicidal Thoughts" is "No", and following 3 items, "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act", "Active Suicidal Ideation with Some Intent to Act, without Specific Plan", "Active Suicidal Ideation with Specific Plan and Intent" are all null, all of these 3 items will be set to "No". This is based on a logic which these 3 items supposed to be followed only by a case of "Yes" in "Non-Specific Active Suicidal Thoughts".

The number and percentage of subjects with suicidal ideation and suicidal behavior

will be summarized by treatment group for all regions and by country for the double-blind treatment phase on the safety population and for the DSP-5423P treatment period on the DSP-5423P dosed population.

7.7.4 Skin Irritation Assessment

Skin irritation will be summarized by counts and percentage in each category for the double-blind treatment phase on the safety population and DSP-5423P treatment period on the DSP-5423P dosed population: Negative, Faint erythema, Erythema, Erythema and Edema, Erythema + Edema + Papules, Serous papules, Vesicles and Coalescing vesicles. Maximum severity based on all post-baseline visits up to and including LOCF endpoint will be also summarized as well as other visits. Summaries will be repeated by country.

7.7.5 Laboratory Evaluations

Data for the following hematology, blood chemistry, and urinalysis parameters received from the central laboratory will be listed and summarized by treatment group and visit including LOCF endpoints for the double-blind treatment phase using the safety population and for the DSP-5423P treatment period on the DSP-5423P dosed population. Observed values and changes from baseline will be summarized.

Hematology	Blood Chemistry	Urinalysis
1. white blood cell count, 2. red blood cell count, 3. hemoglobin, 4. hematocrit, 5. platelet count, 6. neutrophils, 7. eosinophils, 8. basophils, 9. monocytes, 10. lymphocytes	1. total protein, 2. total bilirubin, 3. AST, 4. ALT, 5. ALP, 6. γ-GTP, 7. LDH, 8. total cholesterol, 9. triglycerides, 10. BUN, 11. creatinine, 12. CK, 13. Na, 14. K, 15. Cl, 16. blood glucose, 17. HbA1c, 18. serum prolactin	1. glucose, 2. protein, 3. occult blood, 4. urobilinogen

All laboratory data will be reported in conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" sign (i.e. those below the limits of quantification) will be set as missing. If values preceded by a ">" sign (i.e., those above the limits of quantification) are observed, handling will be discussed at BDRM. Note that these values with a "<" or ">" sign will be presented values as reported from the laboratory in the listing.

Mean change from baseline to Week 6 (LOCF) in selected parameters, which are serum prolactin concentration, glucose and HbA1c, will be analyzed using a nonparametric rank ANCOVA. For each pairwise comparison versus placebo, values of the change from baseline at LOCF endpoint and baseline values will be ranked. A linear regression will be conducted on the ranked change from baseline with ranked baseline value as independent variable to produce regression residuals. Using the values of the residuals as scores, Mantel-Haenszel row mean score tests will be produced for each DSP-5423P group versus placebo (Stokes, Davis, & Koch, 1995).

```
* compute the ranks of the response variable and covariate;
proc rank data = &ads out=ranks npuls12 ties=mean;
  var chg base;
  ranks rkchg rkbase;
```

```
run;
* calculate the residuals from the linear regression;
proc glm data=ranks;
  model rkchg=rkbase;
  output out=residual r=resid;
run;
* CMH mean score statistics are used to compare the groups;
proc freq data=residual;
  tables trt01p*resid / cmh2;
  ods output diffs=diff;
run;
```

Markedly Abnormal Post-Baseline Laboratory Values (MAPLV) for selected laboratory parameters can be found in Table 1. The criterion of MAPLV is satisfied if a value falls into the markedly abnormal range. Subjects will be represented in the count of a particular MAPLV if they have experienced that MAPLV at least once in the post-baseline (including unscheduled visits), regardless of baseline value, up to and including LOCF endpoints and repeat for each country. Only parameters with MAPLV throughout the study period per subject will be listed.

Table 1 Criteria for Markedly Abnormal Post-Baseline Laboratory Values

Hematology Parameter	Markedly Abnormal Range
Hemoglobin	Male: ≤ 11.5 g/dL
	Female: ≤ 9.5 g/dL
Hematocrit	Male: ≤ 37%
	Female: ≤ 32%
WBC	≤ 2.8 x 10^3/uL
	≥ 16 x 10^3/uL
Platelets	≤ 75 x 10^3/uL
	≥ 700 x 10^3/uL
Chemistry Parameter	**Markedly Abnormal Range**
ALT	≥ 3 x ULN
AST	≥ 3 x ULN
Alkaline Phosphatase	≥ 1.5 x ULN
Na/Sodium	< 130 mEq/L
	> 150 mEq/L
K/Potassium	< 3 mEq/L
	> 5.5 mEq/L
Cl/Chloride	< 90 mEq/L
	> 115 mEq/L

Blood Glucose (fasting)	< 50 mg/dL
	> 250 mg/dL
HbA1c	≥ 7.5%
Total Bilirubin	> 2 x ULN
Blood Urea Nitrogen	> 30 mg/dL
Creatinine	> 2.0 mg/dL
CK	> 3 x ULN
Serum Prolactin	≥ 5 x ULN
Triglycerides (fasting)	> 300 mg/dL
Total Cholesterol (fasting)	> 300 mg/dL

Box plot of observed value of the hematology and blood chemistry parameters will be provided for the double-blind treatment phase and the DSP-5423P treatment period by the treatment group and visit.

7.7.6 Vital Signs and body weight

The following vital signs as well as body weight and BMI will be listed and summarized by treatment group and visit including LOCF endpoints for double blind phase using the safety population and for the DSP-5423P treatment period using the DSP-5423P dosed population. Observed values and change from baseline values will be summarized in descriptive statistics:

- Sitting systolic blood pressure (mmHg);
- Sitting diastolic blood pressure (mmHg);
- pulse rate (beats/min);
- body temperature (°C).

Markedly Abnormal Post-Baseline Vital Signs (MAPVS) are defined in Table 2. Subjects will be represented in the count of a particular MAPVS if they have experienced that MAPVS at least once in the post-baseline (including at unscheduled visits), regardless of baseline value, up to and including LOCF endpoints for the double blinded phase using the safety population and the DSP-5423P treatment period using the DSP-5423P dosed population. The subjects with parameter met MAPVS criterion will be listed.

Table 2: Criteria for Markedly Abnormal Post-Baseline Vital Signs

Parameter	Markedly low	Markedly high
Weight	≥ 7% decrease from Baseline	≥ 7% increase from Baseline

Box plot of observed value of the vital signs and body weight will be provided for the double-blind treatment phase and the DSP-5423P treatment period by the treatment group and visit.

7.7.7 Electrocardiograms

ECG parameters (RR interval, QT interval, PR interval, QRS interval, and QTc interval (QTc Fridericia [QTcF] and QTc Bazett [QTcB]) will be listed and summarized by treatment group and visit including LOCF endpoints for the double-blind treatment phase using the safety population and for the DSP-5423P treatment period using the DSP-5423P dosed population. Observed values and change from baseline values will be summarized.

Similarly, interpretation of ECG (normal, abnormal) will be listed and summarized as frequency and percentage by treatment group and visit including LOCF endpoints. Shift from baseline will be summarized as well. Findings of ECG will be listed. If irregular interpretation is obtained, for example "Not evaluable", it will be set to missing.

QT prolongations are defined in Table 3. For each criterion, subject with abnormal value at least once in the post-baseline (including unscheduled visits) will be identified for the double-blind treatment phase using the safety population and for the DSP-5423P treatment period for the DSP-5423P dosed population. Frequency and percentage of subjects with QT prolongation for each criterion will be summarized by treatment group.

Table 3: QT Prolongation

Parameter	QTc Prolongation
QTcB, QTcF	> 450 msec
QTcB, QTcF	> 480 msec
QTcB, QTcF	> 500 msec
QTcB, QTcF	> 30 msec increased from baseline
QTcB, QTcF	> 60 msec increased from baseline

7.7.8 Subgroup Analysis

Subgroup analysis will be performed for TEAE and Summary Statistics of DIEPSS total score (excluding overall severity). Subgroup analysis will include sex, age, race (only TEAE), and country and will be done for the double-blind treatment phase using the safety population and for DSP-5423P treatment period for the DSP-5423P dosed

population. Age will be dichotomized as less than 65 years and older than or equal to 65 years.

C-SSRS will also be summarized by country as specified in 7.7.1.

For the double-blind treatment phase, subgroup analyses of before and after the interim analysis will also be performed for adverse events where the before subgroup will consist of the subjects included in the interim analysis (1st to 251st randomized subjects) and the after subgroup consists of the remaining subjects.

7.8 Pharmacokinetic Analysis

Summary statistics of plasma concentrations of blonanserin and M-1, and ratio of plasma concentration of M-1 to blonanserin (ie, M1/blonanserin) will be calculated for the PK population at Week 1, 2, and 6 in the double-blind treatment phase by treatment group and at Open-Week 28 (Week 34) and Open-Week 52 (Week 58) in the open-label treatment phase by the latest dose prior to the PK sampling. Summary statistics will include n, mean, SD, CV%, maximum, median, minimum, geometric mean, and geometric CV%. Treatment groups for the double-blind treatment phase will be 40MG and 80MG group. For the open-label treatment phase, concentrations and ratios will be summarized by the latest dose prior to the PK sampling (ie, 40, 60, or 80 MG).

Data below detection limit will be handled as missing and not be included in summary statistics, but the listing.

Summary statistics of plasma concentration of blonanserin, M1, and their ratio at each dose will also be summarized by subgroup. Subgroups will include sex, age group, application site, race, and country. Age will be dichotomized as less than 65 years (non-elderly) and older than or equal to 65 years (elderly).

Subgroup will further be examined for plasma concentration of blonanserin and M1 at Week 6 in the double-blind treatment phase and at Open-Week 28 (Week 34) in the open-label treatment phase. The ratio of the geometric means and the corresponding 90% confidence intervals will be estimated for the ratios of elderly/non-elderly, female/male, each country/Japan, and each race/Asian, Plasma concentrations will be natural log transformed and analyzed by a linear model, then the estimates for difference between subgroups and their confidential intervals will be back-transformed (ie, using exponential function) to obtain the estimates for the ratio. The model will include treatment (or the latest dose) and subgroup as fixed effects.

```
proc mixed;
  class dose sex age country race;
  model ln_pc = dose age sex country race;
  lsmeans dose age sex country race/ diff=control ('40', '0', 'Male',
'Japan', 'Asian') cl alpha=.10;
run;
```

7.9 Interim Analysis, Interim Data Summary, and Final Analysis

An unblinded interim analysis for futility will be performed after 50% of target number of subjects complete or prematurely discontinue the double-blind treatment phase. The interim analysis will be performed on the change in PANSS total score from baseline in the mITT population. If the conditional power based on the treatment differences in PANSS total score is less than the futility criteria of 8%, the study may be terminated early. Otherwise, the study will be continued. The interim analysis will be conducted based on the charter for the interim analysis and an interim analysis plan, separately from this document.

Apart from the formal interim analysis, after all subjects have completed the double-blind treatment phase or prematurely terminated the study, the efficacy and safety data up to 6 weeks will be analyzed. After all subjects have completed at Visit 108 (Open-Week 24) in the open-label treatment phase or discontinued from the study, the study data will be analyzed for the purpose of the regulatory submission before the database lock.

The unblinded analysis after the completion of the double-blind treatment phase will be limited for the analyses for this phase, based on the database for double-blind treatment phase (EDC for this phase), and using the mITT, PP, safety and PK populations. These analysis populations and important protocol deviations in the double-blind treatment phase will be determined in a blinded data review prior to unblinding. However only subject assignment to PK population in the double-blind treatment phase will be finalized after unblinding, and PK data is obtained and reviewed by the study team.

After completion of Visit 108, the database for double-blind treatment phase and open-label treatment phase will be combined to analyze the DSP-5423P treatment period using the DSP-5423P dosed population as well as the open-label population. The analysis will be limited for data from Visit 101 (Open-Week 1) to Visit 108 (Open-

Week 24) including discontinuation and unscheduled visits during Visit 101 to 108. Adverse events and concomitant medications occurred or started on or after Open Day 177 or later will not be included. The DSP-5423P dosed population and the open-label population and important protocol deviations for the open-label treatment phase up to Visit 108 will be determined prior to the data lock for the interim data summary.

The final analysis will be conducted after the completion of the study and will include all data. Important protocol deviations will also be reviewed prior to the final database lock at the conclusion of the study.

In case of the early termination of the study based on the interim analysis, final data analysis will be performed once after the completion of the entire study, ie, early termination and capturing all the study data as required by the study protocol.

7.10 Others

In case that any subjects need to be excluded from all analysis, based on blind data review prior to data base lock, only relevant listings including these subjects will be produced.

8 CHANGES IN PLANNED ANALYSES

Not applicable.

9 DATA ISSUES

Not applicable.

10 REFERENCES

1. Garcia E, Robert M, Peris F, Nakamura H, Sato N, Terazawa Y(2009). The efficacy and safety of blonanserin compared with haloperidol in acute-phase schizophrenia.CNS Drugs, 23(7):615-25.
2. Kemp AS, Schooler NR, Kalali AH, Alphs L, Anand R, Awad G, et al (2010). What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it?. Schizophrenia Bulletin,36:504-9.
3. Lindenmayer JP, Bernstein-Hyman R, Grochowski S (1994). A new five factor model of schizophrenia. Psychiatric Quarterly, 65(4):299-322.
4. Hochberg Y (1988). A Sharper Bonferroni Procedure for Multiple Tests of Significance. Biometrika, 75 (4): 800–802.

5. Stokes, M., Davis, C., & Koch, G. (1995). Categorical Data Analysis using the SAS system. Cary, NC: SAS Institute Inc.
6. O'Kelly M and Ratitch B. Clinical Trials with Missing Data. A Guide for Practitioners. Wiley; 2014

11 APPENDICES

Appendix I - Schedule of Events

Table 4 Schedule of Assessments (Double-blind treatment phase)*

			Washout phase (1 week)	Double-blind treatment phase (6 weeks)				
Visit No.	-	1	-	2	3	4	5	6
Study timeline [a]	-	Screening	Week -1	Day 1	Week 1	Week 2	Week 4	Week 6
Visit window (Day)		−21 ~ −4	−7 ~ −3	−2 ~ 1	5 ~ 11	12 ~ 18	26 ~ 32	40 ~ 43
Obtain informed consent	X							
Hospitalization [b]		◄	———	———	———	——►	- - - - -	- - - - - ►
Patient demographics and medical history		X						
Inclusion/ Exclusion criteria assessments		X		X				X
Randomization [c]				X				
Dispense study drug		X		X	X	X	X	X[f]
Study treatment compliance				X	X	X	X	X
PANSS		X		X	X	X	X	X[g]
CGI-S		X		X	X	X	X	X[g]
DIEPSS				X	X	X	X	X[g]
C-SSRS				X	X	X	X	X[g]
Skin irritation assessment				X	X	X	X	X
Laboratory test [d]		X		X		X		X[g]
Pregnancy test [e]		X						X
12-lead ECG		X		X	X	X		X[g]
Body weight		X		X	X	X	X	X
Body temperature, blood pressure, pulse rate		X		X	X	X	X	X
Adverse event monitoring			◄	———	———	———	———	——►
Blood sampling for PK					X	X		X[g]

a Day 1 is defined as the day of the initial application of the study drug in the Double-blind treatment phase, and Day −1 is defined as the day before Day 1.
b All subjects will be hospitalized from screening until Day 14 (Visit 4). After Day 14 and completion of assessments at Visit 4, a subject who meets the criteria can be an outpatient.
c Subjects will be randomized after scheduled assessments at Visit 2 are completed.
d All blood samples will be collected under fasting conditions (at least 10 hours after the last meal).
e To be performed only in female subjects who are premenopausal and of childbearing potential.
f The study drug for the Open-label treatment phase will be dispensed.
g Must be performed before the initial application of study drug in the Open-label treatment phase.

* If a subject discontinues the study drug during the washout phase, the subject will undergo the following safety assessments: study treatment compliance, skin irritation assessment, laboratory test, 12-lead ECG, body weight, body temperature, blood pressure, pulse rate, and adverse event monitoring at the discontinuation visit in Table 5 or Table 6. If a subject discontinues the study drug after entering the Double-blind treatment phase, the subject

will undergo the discontinuation visit and the follow-up visit in Table 5 or Table 6.

Table 5 Schedule of Assessments for outside Japan (Open-label treatment phase)

	Double-blind treatment phase	Open-label treatment phase (28 weeks)									Discontinuation	Follow-up phase (1-2 weeks)
Visit No.	6	101	102	103	104	105	106	107	108	109	Discontinuation visit	Follow-up visit
Timeline from the beginning of the Open-label treatment phase [a] (Study timeline)	- (Week 6)	Open-Week 1 (Week 7)	Open-Week 2 (Week 8)	Open-Week 4 (Week 10)	Open-Week 8 (Week 14)	Open-Week 12 (Week 18)	Open-Week 16 (Week 22)	Open-Week 20 (Week 26)	Open-Week 24 (Week 30)	Open-Week 28 (Week 34)	-	-
Visit window in the Open-label treatment phase (Day)	-	Open-5-11	Open-12-18	Open-26-32	Open-50-64	Open-78-92	Open-106-120	Open-134-148	Open-162-176	Open-190-204	At discontinuation +5	6-17 days after completion of treatment or discontinuation
Hospitalization [b]	◄----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------►
Inclusion/ Exclusion criteria assessments	(X)											
Dispense study drug	(X)	X	X	X	X	X	X	X	X			
Study treatment compliance	(X)	X	X	X	X	X	X	X	X	X	X	
PANSS	(X)	X	X	X	X	X	X	X	X	X [e]	X [e]	
CGI-S	(X)	X	X	X	X	X	X	X	X	X [e]	X [e]	
DIEPSS	(X)	X	X	X	X	X	X	X	X	X [e]	X [e]	
C-SSRS	(X)	X	X	X	X	X	X	X	X	X [e]	X [e]	
Skin irritation assessment	(X)	X	X	X	X	X	X	X	X	X	X	
Laboratory test [c]	(X)			X		X		X		X [e]	X [e]	
Pregnancy test [d]	(X)									X	X	
12-lead ECG	(X)			X		X		X		X [e]	X [e]	
Body weight	(X)	X	X	X	X	X	X	X	X	X	X	
Body temperature, blood pressure, pulse rate	(X)	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring	◄----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------►
Blood sampling for PK	(X)									X [e]	X [e]	

a Open-Day 1 is defined as the day of the initial application of the study drug in the Open-label treatment phase.
b All subjects can be inpatients or outpatients.
c At Visit 109 and at the discontinuation visit, blood samples will be collected under fasting conditions (at least 10 hours after the last meal). At other visits, blood samples should be collected under fasting conditions (at least 10 hours after the last meal) whenever possible.
d To be performed only in female subjects who are premenopausal and of childbearing potential.
e Must be performed before the beginning of post-treatment with antipsychotics excluding the study drug.

Table 6 Schedule of Assessments for Japan (Open-label treatment phase)

	Double-blind treatment phase	Open-label treatment phase (52 weeks)												Discontinuation	Follow-up phase (1-2 weeks)
Visit No.	6	101	102	103	104	105	106	107	108	109	110	111	112	Discontinuation visit	Follow-up visit
Timeline from the beginning of the Open-label treatment phase [a] (Study timeline)	- (Week 6)	Open-Week 1 (Week 7)	Open-Week 2 (Week 8)	Open-Week 4 (Week 10)	Open-Week 8 (Week 14)	Open-Week 12 (Week 18)	Open-Week 16 (Week 22)	Open-Week 20 (Week 26)	Open-Week 24 (Week 30)	Open-Week 28 (Week 34)	Open-Week 36 (Week 42)	Open-Week 44 (Week 50)	Open-Week 52 (Week 58)	-	-
Visit window in the Open-label treatment phase (Day)	-	Open-5-11	Open-12-18	Open-26-32	Open-50-64	Open-78-92	Open-106-120	Open-134-148	Open-162-176	Open-190-204	Open-239-267	Open-295-323	Open-351-379	At discontinuation +5	6-17 days after completion of treatment or discontinuation
Hospitalization [b]	←	----	----	----	----	----	----	----	----	----	----	----	----	----	---→
Inclusion/ Exclusion criteria assessments	(X)														
Dispense study drug	(X)	X	X	X	X	X	X	X	X	X	X	X			
Study treatment compliance	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	
PANSS	(X)	X	X	X	X	X	X	X	X	X	X	X	X [e]	X [e]	
CGI-S	(X)	X	X	X	X	X	X	X	X	X	X	X	X [c]	X [c]	
DIEPSS	(X)	X	X	X	X	X	X	X	X	X	X	X	X [e]	X [e]	
C-SSRS	(X)	X	X	X	X	X	X	X	X	X	X	X	X [c]	X [c]	
Skin irritation assessment	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory test [c]	(X)			X		X		X		X	X	X	X [c]	X [c]	
Pregnancy test [d]	(X)												X	X	
12-lead ECG	(X)			X		X		X		X	X	X	X [c]	X [c]	
Body weight	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body temperature, blood pressure, pulse rate	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring	←	----	----	----	----	----	----	----	----	----	----	----	----	----	---→
Blood sampling for PK	(X)									X			X [c]	X [c]	

a Open-Day 1 is defined as the day of the initial application of the study drug in the Open-label treatment phase.
b All subjects can be inpatients or outpatients
c At Visit 112 and at the discontinuation visit, blood samples will be collected under fasting conditions (at least 10 hours after the last meal). At other visits, Blood samples should be collected under fasting conditions (at least 10 hours after the last meal) whenever possible.
d To be performed only in female subjects who are premenopausal and of childbearing potential.
e Must be performed before the beginning of post-treatment with antipsychotics excluding the study drug.

Appendix II - Pooled centers

COUNTRY	SITEID	N of Randomized subjects	N per pooled center	Pooled center ID
Japan	101	2	25	P101
	102	3		
	103	1		
	104	3		
	105	5		
	106	5		
	107	1		
	108	3		
	109	2		
	110	7	28	P102
	111	3		
	112	7		
	113	2		
	114	1		
	115	3		
	116	1		
	118	4		
	117	12	12	P103
	119	3	30	P104
	120	1		
	121	3		
	122	4		
	123	6		
	124	5		
	125	2		
	126	6		
	127	1	29	P105
	129	5		
	130	1		
	131	2		
	132	5		
	134	6		
	135	3		
	137	3		
	138	3		
	139	3	24	P106
	140	2		
	141	5		
	143	4		
	144	2		

	146	8		
	147	3	16	P107
	148	3		
	149	3		
	152	3		
	154	1		
	155	3		
Korea	201	2	21	P201
	203	6		
	204	4		
	205	1		
	206	6		
	207	2		
Taiwan	301	8	28	P301
	302	7		
	304	8		
	305	3		
	306	2		
	303	18	18	P302
Malaysia	401	20	20	P401
	402	19	19	P402
	403	3	19	P403
	409	3		
	411	5		
	412	4		
	413	1		
	414	3		
	404	34	34	P404
	406	15	15	P405
	407	12	12	P406
	408	28	28	P407
	410	11	11	P408
	415	11	11	P409
Philippine	501	9	23	P501
	502	4		
	505	10		
	503	20	20	P502
	504	11	11	P503
	506	7	15	P504
	507	5		
	508	2		
	509	1		
China	601	5	13	P601
	602	8		

	603	15	15	P602
Russia	702	6	26	P701
	703	7		
	704	4		
	705	3		
	706	6		
	707	6	13	P702
	708	7		
	801	10	18	P801
Ukraine	802	1		
	803	7		
	805	4	17	P802
	806	7		
	807	6		
	809	11	11	P803
Total		582	582	