DSP-5423P

Blonanserin

D4904020

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

Version 2.04

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EMERGENCY CONTACTS

Table 1 Emergency Contact Information (outside Japan)

Role in Study	Name	Contact Information
Medical Monitor	[redacted]	[redacted]
	[redacted]	[redacted]
SAE/Pregnancy Reporting	[redacted]	[redacted]

Table 2 Emergency Contact Information (in Japan)

Role in Study	Name	Contact Information
Responsible monitor (SAE/Pregnancy Reporting)	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor:	Sumitomo Dainippon Pharma. Co., Ltd.
Name of Investigational Product:	DSP-5423P (transdermal patches)
Name of Active Ingredient:	Blonanserin
Title of Study: Confirmatory Study of DSP-5423P in Patients with Schizophrenia <Phase 3>	
Proposed Indication:	Schizophrenia
Phase of Development:	Phase 3
Study period (planned):	August 2014 ~ December 2018

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.

Study Design:

Double-blind treatment phase

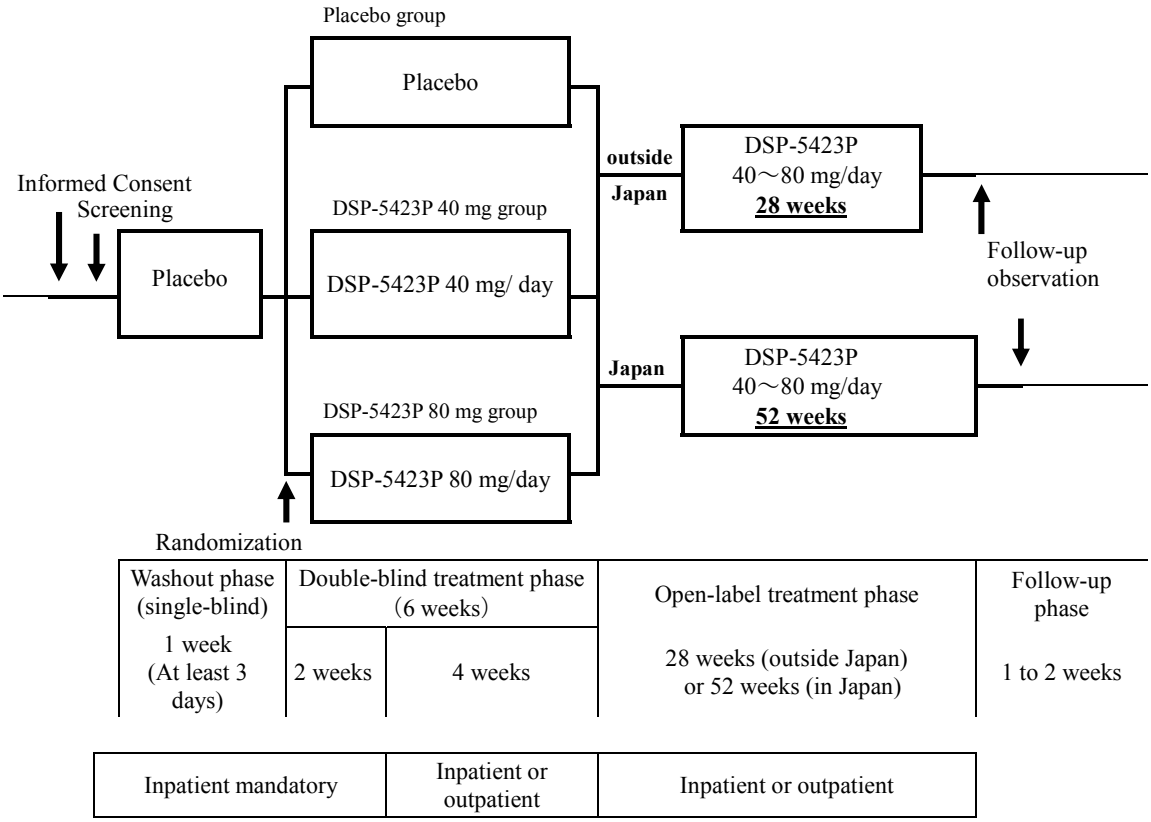
Multicenter, randomized, double-blind, placebo-controlled, parallel-group

Open-label treatment phase

Multicenter, open-label, flexible dose

The unblinded interim analysis for futility will be performed after 50% of target number of subjects complete or prematurely discontinue the double-blind treatment phase.

Study schematic



Number of Subjects (planned):

501 subjects will be randomized to 3 treatment groups (167 subjects in each treatment group) in double-blind treatment phase. Only subjects who have completed the 6-week double-blind treatment phase without any safety concerns can enter the open-label treatment phase.

Diagnosis:

Schizophrenia

Criteria for Subject Inclusion at screening:

＜The procedure in Japan is described in the Japan Appendix.>

Patients who meet all the following criteria at screening will be included in the study:

1. Patients who have schizophrenia diagnosed by Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), diagnostic criteria
2. Patients who have psychiatric symptoms (eg, aggravated delusions) with schizophrenia showing exacerbation within 2 months (60 days) before screening
3. Patients with a PANSS score of 4 (moderate) or higher for 2 or more of the following 5 items: delusions (P1), conceptual disorganization (P2), hallucinations (P3), suspiciousness (P6), and unusual thought content (G9)
4. Patients with a total PANSS score of 80 or higher
5. Patients who can be hospitalized from screening until the scheduled date of Visit 4
6. Patients who are aged 18 years or older at informed consent
7. Patients who are fully informed of and understand the objectives, procedures, and possible benefits and risks of the study and who voluntarily provide written consent to participate in the study. If the patient is a minor at informed consent, written consent will be obtained from a legally acceptable representative[Note] in addition to that obtained from the patient.

   Note: A legally acceptable representative is defined as a person within the second degree of kinship, in principle, who can act in the patient's best interest in the context of daily lifestyle and the existing mental relationship between the two parties.

8. Female patients, who are premenopausal and of childbearing potential, with negative pregnancy test (urine) results at screening
9. Patients who agree to practice appropriate contraception, when the patients or their partners are of childbearing potential

Criteria for Subject Exclusion at screening:

Patients who meet any of the following criteria will be excluded from the study.

1. Patients in a coma
2. Patients under the strong influence of central nervous system depressants such as barbituric acid derivatives
3. Patients receiving treatment with adrenaline, azole antifungals (excluding drugs for external use), or human immunodeficiency virus (HIV) protease inhibitors
4. Patients with a history of or current neuroleptic malignant syndrome, tardive dyskinesia, or water intoxication
5. Patients with Parkinson's disease
6. Patients with active suicidal ideation or those with a suicide attempt history who

are considered ineligible for the study by the Investigator

7. Patients with HbA1c (NGSP) of 8.4% or higher
8. Patients with physical exhaustion accompanied by conditions such as dehydration and malnutrition
9. Patients with a history of or complication(s) involving serious cardiovascular, hepatic, renal, organic brain, hematologic, endocrine, convulsive disease or other conditions, and who are considered ineligible for the study by the Investigator
10. Patients with skin injuries, skin diseases or tattoos that preclude the application of the study drug to the back, chest, or abdomen
11. Patients with a history of drug abuse, drug dependency, alcohol abuse, or alcohol dependency within 6 months (180 days) before screening
12. Patients who received any depot preparation (sustained-release formulation) of an antipsychotics within 3 months (90 days) before screening
13. Patients who received clozapine within 4 months (120 days) before screening
14. Patients who are considered resistant to treatment for psychiatric symptoms by the Investigator. Treatment resistance is defined as failure to respond to 3 or more antipsychotics within 1 year (365 days) before screening
15. Patients who previously received blonanserin
16. Patients who received monoamine oxidase (MAO) inhibitors or fluoxetine within 1 month (30 days) before screening
17. Patients who received electroconvulsive therapy within 6 months (180 days) before screening
18. Patients who are pregnant, or are nursing mothers
19. Patients with a history or complication(s) of hypersensitivity to 2 or more drugs (patients with a history or complication(s) of drug-induced allergic reactions such as anaphylaxis, rash, and urticaria)
20. Patients with a history or complication(s) of malignant tumor within 5 years before screening
21. Patients who are currently infected with HIV
22. Patients who received other investigational products or post-marketing clinical study drugs within 3 months (90 days) before screening or who have enrolled in but have not completed another clinical or post-marketing study before screening
23. Patients who are otherwise considered ineligible for the study by the Investigator

Criteria for Subject Inclusion before randomization:

Subjects who meet all the following criteria before randomization (at Visit 2) will be randomized.

1. Subjects with a PANSS score of 4 (moderate) or higher for 2 or more of the following 5 items: delusions (P1), conceptual disorganization (P2), hallucinations (P3), suspiciousness (P6), and unusual thought content (G9)
2. Subjects with a PANSS total score of 80 or higher

Criteria for Subject Exclusion before randomization:

Subjects who meet any of the following criteria will be excluded from the study before randomization.

1. Subjects with a 20% or more reduction in the PANSS total score between screening and randomization (at Visit 2)

$$\left(\frac{\text{PANSS total score at screening} - \text{PANSS total score at randomization}}{\text{PANSS total score at screening} - 30} \right) \times 100 \geq 20\%$$

2. Subjects who are otherwise considered ineligible for the study by the Investigator

Criteria for Subject Inclusion before the open-label treatment phase:

Subjects who meet the following criterion will enter the open-label treatment phase.

1. Subjects who have completed the 6-week study treatment and all scheduled assessments at Visit 6 in the double-blind treatment phase, and who are considered eligible by the Investigator with no safety concerns

Criteria for Subject Exclusion before the open-label treatment phase:

Subjects who meet any of the following criteria will be excluded from the study before the open-label treatment phase.

1. Subjects who are planning to become pregnant at any time before the end of the follow-up phase
2. Subjects who are otherwise considered ineligible for the study by the Investigator

Investigational Product: DSP-5423P (transdermal patches)

Reference Therapy: Placebo

Dosage and Mode of Administration:

The double-blind treatment phase

DSP-5423P 40 mg, 80 mg, or placebo will be applied to the back, chest, or abdomen once daily.

The open-label treatment phase

DSP-5423P will be applied to the back, chest, or abdomen once daily as flexible dose (40, 60, or 80 mg)

Duration of Treatment:

The double-blind treatment phase 6 weeks

The open-label treatment phase 28 weeks (outside Japan) or 52 weeks (in Japan)

Concomitant Medications:

See Section 10.3 Concomitant Medications and Therapies (p38) for further information

Restrictions on concomitant medications/therapies from screening until the end of the follow-up phase

	From screening before the washout phase	Washout phase	Double-blind treatment phase	Open-label treatment phase	Follow-up phase
Antipsychotics	B	A	A	B	C
Antimanic and antiepileptic drugs	A	A	A	B	C
MAO inhibitors	A	A	A	A	C
CYP3A4 inhibitors (External drugs for topical use can be used.)	A	A	A	A	A
CYP3A4 inducers (External drugs for topical use can be used.)	A	A	A	A	C
Adrenaline (excluding use for emergency treatment of anaphylaxis)	A	A	A	A	A
Other investigational products or post-marketed study products	A	A	A	A	A
Electroconvulsive therapy	A	A	A	A	C
Antiparkinson drugs	B	B	B	B	C
Psychotropic drugs (eg, anxiolytic drugs, antidepressants)	B	B	B	B	C
Hypnotic drugs	B	B	B	B	C
Treatments for complications	B	B	B	B	C

A, prohibited; B, restricted; C, unrestricted

Abbreviations: MAO=Monoamine oxidase; CYP3A4=Cytochrome P-450 enzyme 3A4

Study Endpoints:

Primary Endpoint:

The primary endpoint is the change in PANSS total score from baseline at Week 6.

Secondary Endpoints:

- Change in PANSS subscale scores from baseline at Week 6
- Change in PANSS five-factor model scores from baseline at Week 6
- Change in Clinical Global Impressions - Severity of Illness (CGI-S) score from baseline at Week 6
- Change in PANSS total score from the last evaluation before the initial application of DSP-5423P at each visit
- Change in PANSS subscales from the last evaluation before the initial application of DSP-5423P at each visit
- 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
- Change in CGI-S score from the last evaluation before the initial application of DSP-5423P at each visit
- Time to treatment discontinuation from the initial application in the open-label treatment phase

Safety Endpoints:

- 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
- Change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total score (excluding overall severity) from baseline at Week 6
- Change in individual DIEPSS scores from baseline at Week 6
- Change in DIEPSS total score (excluding overall severity) from the last evaluation before the initial application of DSP-5423P at each visit
- 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

Pharmacokinetics Endpoints:

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

Statistical Methods:

Primary analysis:

The primary analysis will be conducted on the modified intention-to-treat (mITT) population, which includes all subjects who are randomized, apply the study drug at least once in the double-blind treatment phase, and have a baseline and at least one post-baseline PANSS total score rated in the double-blind treatment phase.

The primary efficacy variable for comparing the DSP-5423P 40 and 80 mg/day versus placebo is the change in PANSS total score from baseline at Week 6. A mixed model for repeated measures (MMRM) will be used for the primary efficacy analysis. The MMRM model will include treatment, visit, and pooled study center as categorical factor, baseline PANSS total score as covariate, and treatment-by-visit interaction. An unstructured covariance matrix will be used for the within-subject correlation. Missing observations will not be imputed for this analysis.

The Hochberg procedure will be used to control the overall type I error at 5% by taking into account multiple dose regimens for the primary efficacy analysis.

Interim 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.

Sample Size:

Effect size of DSP-5423P is estimated 0.45 for both DSP-5423P 40 and 80 mg/day versus placebo (See Section 15.1 Sample Size Determination). A sample size of 133 per group was estimated to yield a complete power (probability of rejecting both two null hypotheses) of 89% with a two-sided alpha of 5% significance level using the Hochberg procedure for multiplicity adjustment and taking an interim analysis for

futility into consideration. The sample size was calculated by a Monte-Carlo simulation using SAS software (SAS Instititute). Considering that there is possibility of patients discontinuing before completion of the double-blind treatment phase, the total sample size will need to be 501 patients or 167 patients per treatment group.

Table 3 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 4 outside Japan or that in Table 5 in Japan.

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 4 outside Japan or that in Table 5 in Japan. However, if a subject completes the double-blind treatment phase and discontinues before entering the open-label treatment phase, the subject will undergo the follow-up visit in Table 4 or that in Table 5.

Table 4 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 [f]	6-17 days after completion of treatment or discontinuation [g]
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.
f Discontinuation is defined as the last date of study drug application. The subject will undergo the discontinuation assessments within 5 days since the last date of study drug application.
g Completion of treatment or discontinuation is defined as the last date of study drug application. The subject will undergo the follow-up assessments in 6 - 17 days since the last date of study drug application.

Table 5 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 [f]	6-17 days after completion of treatment or discontinuation [g]
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 [e]	X [e]	
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 [e]	X [e]	
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 [e]	X [e]	
Pregnancy test [d]	(X)												X	X	
12-lead ECG	(X)			X		X		X		X	X	X	X [e]	X [e]	
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 [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 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.
f Discontinuation is defined as the last date of study drug application. The subject will undergo the discontinuation assessments within 5 days since the last date of study drug application.
g Completion of treatment or discontinuation is defined as the last date of study drug application. The subject will undergo the follow-up assessments in 6 - 17 days since the last date of study drug application.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definitions of key study terms used in the clinical study protocol are shown in Table 6.

Table 6 List of Abbreviations

Abbreviation	Full Form
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
CGI-S	Clinical Global Impression – Severity of Illness
CK	Creatine phosphokinase
Cl	Chlorine
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P-450 enzyme
DIEPSS	Drug-Induced Extrapyramidal Symptoms Scale
DMC	Data monitoring committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiogram
EDC	Electronic data capture
γ-GTP	γ-Glutamyltranspeptidase
HbA1c	Hemoglobin A1c
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IPDs	Important protocol deviations
IVRS/IWRS	Interactive voice response system/ Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
MAO	Monoamine oxidase
mITT	modified Intention-to-treat population
MMRM	Mixed Model for Repeated Measurement
Na	Sodium
NGSP	National Glycohemoglobin Standardization Program
PANSS	Positive and Negative Syndrome Scale

Abbreviation	Full Form
PET	Positron emission tomography
PP	Per-Protocol population
QTc	QT interval corrected for heart rate
SC	Steering committee
SDM	Shared decision making
TEAE	Treatment emergent adverse event

4. INTRODUCTION

4.1 Background

Schizophrenia generally appears in puberty or adolescence and is characterized by various psychiatric symptoms including positive symptoms (eg, hallucination, delusion) and negative symptoms (eg, blunted affect, disorganized thinking, lack of motivation). Cognitive symptoms (eg, reduced ability to pursue goals or process information) also occur in some cases. Schizophrenia is a chronic psychiatric disease with repeated relapses which can be triggered by drug refusal and self-medicating.

Therefore, treatment adherence is of interest as a means of symptom control in order to involve patients in decision making processes regarding their therapeutic strategy and pursue aggressive treatment for schizophrenia. Adherence is, however, one of the major challenges in for schizophrenia treatment. Maintaining adherence to treatment is often difficult for patients with schizophrenia[ref.1]. Relapse of schizophrenia or re-hospitalization are mainly caused by poor adherence. Among patients with schizophrenia, 35% of hospitalized patients are deemed non-adherent to medication regimens[ref.2]. Shared decision making (SDM) among physicians and patients regarding their therapeutic strategy is essential for improving adherence. A useful way of implementing SDM may be to provide multiple therapeutic options to patients with schizophrenia and then to make a mutual decision, which takes the patient's opinion into account[ref.3,4].

As factors affecting adherence, environmental, drug and patient factors have all been discussed. Drug formulations have also been emphasized in recent years[ref.2], and various formulations have been or are being developed. Transdermal formulations, which can reduce dosing frequency and invasiveness, are used for treating various diseases. For schizophrenia treatment, however, no transdermal formulations are as yet available anywhere in the world and only injections or oral formulations (eg, tablet, powder, orally disintegrating tablets, liquids) are used.. If a transdermal formulation is available for schizophrenia treatment and is provided to patients as a new option during the SDM process, adherence may be improved [ref.5].

Blonanserin is a second-generation antipsychotic synthesized by Sumitomo Dainippon Pharma Co., Ltd.. Blonanserin, which is a potent antagonist of dopamine D_2 and serotonin 5-HT_{2A} receptors, with a lower affinity for adrenaline α_1, serotonin 5-HT_{2c}, histamine H_1, and muscarinic M_1 receptors[ref.6], is approved and marketed for the treatment of schizophrenia in Japan (tablet and powder formulation) and Korea (tablet

formulation). DSP-5423P, a transdermal blonanserin patch is currently being developed as a new formulation of blonanserin with the aim of improving adherence as described above.

4.2 Study Conduct Rationale

In the clinical study in Japanese healthy adults, 1, 2, or 3 patches of DSP-5423P 32 mg/40 cm^2 were applied to 9 patients each for 24 hours. In addition, 2 patches of DSP-5423P 32 mg/40 cm^2 were applied to 9 patients once daily for 10 days. The results showed that the plasma blonanserin concentration increased depending on the number of patches applied and that the steady state was nearly reached after repeated administration for 7 days.

A new patch formulation, DSP-5423P 20 mg/40 cm^2 was prepared. Pharmacokinetics, after the application of a single patch, were compared between these 2 patch formulations. The results showed that a comparable amount of blonanserin absorption was obtained with these 2 patch formulations. Therefore, the new formulation, DSP-5423P 20 mg/40 cm^2 was used in the following studies.

The phase 2 study of DSP-5423P was conducted in patients with schizophrenia to determine the recommended doses for phase 3 studies. Striatal dopamine D_2 receptor occupancy and plasma drug concentrations after application of DSP-5423P at doses of 10 to 80 mg/day for 2 weeks were compared with results obtained after administration of DSP-5423 (tablet formulation of blonanserin). The results suggest that DSP-5423P 40 mg/day and 80 mg/day may be comparable to DSP-5423 (tablet) 8 mg/day and 16 mg/day, respectively. Since the clinical efficacy of antipsychotics reportedly correlates with dopamine D_2 receptor occupancy[ref.7, 8], DSP-5423P at doses of 40 and 80 mg/day is expected to demonstrate efficacy corresponding to that of DSP-5423 (tablet) at doses of 8 and 16 mg/day, respectively.

In clinical studies of DSP-5423P in healthy adult volunteers or subjects with schizophrenia, no clinically significant adverse events have been reported at doses up to 80 mg, demonstrating tolerability on the skin of application sites.

The phase 3 confirmatory study is designed to be conducted in a randomized, double-blind, placebo-controlled, parallel-group manner. The primary endpoint will be the change in Positive and Negative Syndrome Scale (PANSS) total score from baseline at Week 6. DSP-5423P will be applied for 6 weeks at doses of 40 and

80 mg/day.

In addition, for the subjects who complete the 6-week, double-blind treatment phase of the study, the extensional open-label treatment phase will be conducted to evaluate the long-term safety and efficacy of DSP-5423P at doses of 40 to 80 mg/day.

5. STUDY OBJECTIVES

5.1 Primary Objective

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.

5.2 Secondary Objectives

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.

6. STUDY ENDPOINTS

6.1 Primary Endpoint

The primary endpoint is the change in PANSS total score from baseline at Week 6.

6.2 Secondary Endpoints

- Change in PANSS subscale scores from baseline at Week 6
- Change in PANSS five-factor model[Note] scores from baseline at Week 6
- Change in Clinical Global Impressions – Severity of Illness (CGI-S) score from baseline at Week 6
- Change in PANSS total score from the last evaluation before the initial application of DSP-5423P at each visit
- Change in PANSS subscales from the last evaluation before the initial application of DSP-5423P at each visit
- 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

- Change in CGI-S score from the last evaluation before the initial application of DSP-5423P at each visit
- Time to treatment discontinuation from the initial application in the open-label treatment phase

Note

PANSS five-factor model [ref.9]

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

6.3 Safety Endpoints

- 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
- Change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) total score (excluding overall severity) from baseline at Week 6
- Change in individual DIEPSS scores from baseline at Week 6
- Change in DIEPSS total score (excluding overall severity) from the last evaluation before the initial application of DSP-5423P at each visit
- 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

6.4 Pharmacokinetics Endpoints

- Plasma concentrations of blonanserin

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

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design

A study schematic is presented in Figure 1. The study consists of 4 phases: the washout phase, the double-blind treatment phase, the open-label treatment phase, and the follow-up phase. The double-blind treatment phase is conducted in a multicenter, randomized, double-blind, placebo-controlled, parallel-group manner.

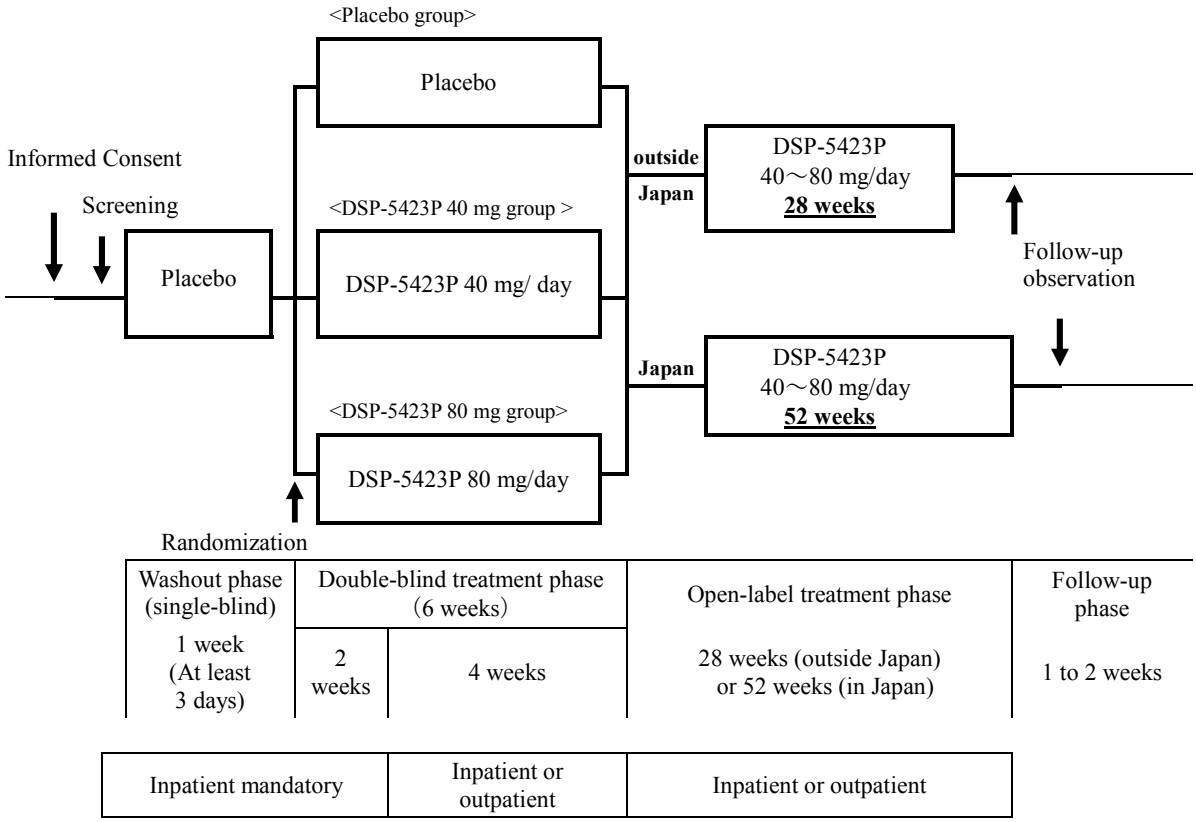
In the washout phase, placebo will be applied once daily for 1 week (at least 3 days) in a single-blind manner. After the washout phase, subjects will be randomized to one of three treatments: 40 mg of DSP-5423P, 80 mg of DSP-5423P, and placebo, at 1:1:1 ratio in the double-blind treatment phase. The study drugs will be applied once daily for 6 weeks. Subjects who complete 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). The study drug will be applied to the back, chest, or abdomen.

Subjects who complete the open-label treatment phase or who prematurely discontinue 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. Details of the study assessments and other procedures to be performed at each visit are presented in Table 3,Table 4, and Table 5 Schedule of Assessments (p10 to 13), and Section11 STUDY ASSESSMENTS (p47).

Day 1 is defined as the day of the initial application of the study drug in the double-blind treatment phase. Open-Day 1 is also defined as the day of the initial application of the study drug in the open-label treatment phase.

After the current study started, an unblinded interim analysis for futility is decided to be performed. The interim analysis will be performed after 50% of target number of subjects complete or prematurely discontinue the double-blind treatment phase. The study will be continued with no temporary suspension of enrollment or randomization of subjects until the Sponsor decides whether to continue or early terminate the study after the interim analysis. Detailed procedure of the interim analysis and the futility criteria are defined in Section15.4 Interim Analysis (p70).

Figure 1 Study Schematic



7.2 Rationale

7.2.1 Rationale for the Study Design

The washout phase is designed to adequately evaluate the efficacy of DSP-5423P by excluding the placebo responders. Since placebo may worsen symptoms, the duration of the washout phase with placebo will be 1 week in principle, but must be at least 3 days. To evaluate long-term efficacy and safety, DSP-5423P will be applied as flexible dose in the open-label treatment phase. To evaluate the safety of a subject after completing or prematurely discontinuing the study drug, the follow-up observations will be performed in 1 to 2 weeks after completion or discontinuation of study treatment, despite the possibility of the study drug being replaced with other antipsychotics.

7.2.2 Rationale for the Dosages

A once-daily regimen was selected since plasma drug concentrations were maintained with minimal change within 24-hour intervals over time in the phase 1 study (Study No. D4904016) of DSP-5423P in Japanese healthy adults.

Striatal dopamine D_2 receptor occupancy after administration of DSP-5423 (tablet) or application of DSP-5423P was evaluated in subjects with schizophrenia by positron emission tomography (PET) in the phase 2 study (Study No. D4904019).

In a comparison of occupancy between subjects treated with 8 mg/day of DSP-5423 (tablet) and those treated with 40 mg/day of DSP-5423P or between subjects treated with 16 mg/day of DSP-5423 (tablet) and those treated with 80 mg/day of DSP-5423P, occupancy after application of DSP-5423P was within the range after administration of DSP-5423 (tablet) at the first (trough) and second (peak) measurements.

The DSP-5423P dose is selected based on the above occupancy results. DSP-5423P doses of 40 mg/day and 80 mg/day are considered to be comparable to DSP-5423 (tablet) at doses of 8 mg/day and 16 mg/day, respectively. DSP-5423 (tablet) at doses ranging from 8 to 16 mg/day is approved for the treatment of schizophrenia. For DSP-5423P, 40 mg/day, and 80 mg/day are to be used in this study.

The duration of the double-blind treatment phase will be 6 weeks, which is commonly used in comparative studies of atypical antipsychotics and is considered sufficient for the efficacy evaluation of these atypical antipsychotics. [ref.10]

From the results of the single dose study (Study No.D4904016) and the location of the application comparative study (Study No.D4904059), the amounts of absorption after application to the chest, the lower back, the upper arm, or the abdomen were comparable to that after application to the upper back. Therefore, the back, chest, and abdomen were selected as the locations of application in this study. The upper arm, which is more likely to be exposed to light, is excluded because DSP-5423P may be a photosensitizer (nonclinical study, No.P110808).

7.2.3 Rationale for the Endpoints

PANSS was selected since it is a comprehensive evaluation scale of the severity of various psychiatric symptoms in schizophrenia, and is frequently used in clinical studies for the evaluation of antipsychotics.[ref10, 11]

7.2.4 Rationale for change of the target number of subjects and the Interim Analysis

After the current study started, the Sponsor reconsidered the statistical power (80%) might not be enough and decided to increase it to approximately 90% with the same

effect size estimates. The target number of subjects is changed from 360 to 501. Considering the increase in the number of subjects exposed to the study drug, to avoid unnecessary exposure of more subjects if an investigational treatment has no value, an unblinded interim analysis for futility is added to the study design.

7.3 Prevention of Missing Data

In an effort to minimize the number of subjects who are terminated from the study before study completion, the following study design and conduct elements are implemented; (i) during the entire study period, concomitant use of antiparkinson drugs, lorazepam, and hypnotic drugs are allowed for extrapyramidal symptoms, psychiatric symptoms, and insomnia respectively, (ii) during the open-label treatment phase, rescue use of antipsychotics is allowed for urgent psychiatric symptoms, (iii) subjects are allowed to be discharged from the study center after Visit 4 (Week 2) or remain in the study center for the entire study duration, based on their medical condition, (iv) during the open-label treatment phase, flexible dose adjustment is allowed based on efficacy or tolerability, (v) use of study centers with a good track record of enrolling and following eligible subjects, (vi) train the study centers on the importance of continued follow-up and on the informed consent process, ensuring subjects understand the commitment they are making, including the intent to complete the trial, and (vii) monitor data collection for adherence during the study.

7.4 Planned Study Period

August 2014 ~ December 2018 (enrollment period, August 2014 ~ September 2017)

8. SELECTION OF SUBJECTS

The Investigator will evaluate patient eligibility for the study at screening, randomization, and before the open-label treatment phase. When a patient is not eligible, the Investigator will specify which inclusion/exclusion criteria to exclude a patient from the study, and record the specified inclusion/exclusion criteria by number in the CRF.

8.1 Criteria at screening

8.1.1 Inclusion Criteria at screening

＜The procedure in Japan is described in the Japan Appendix.>

Patients who meet all the following criteria at screening will be included in the study:

1. Patients who have schizophrenia diagnosed by Diagnostic and Statistical Manual

of Mental Disorders, fifth edition (DSM-5), diagnostic criteria

2. Patients who have psychiatric symptoms (eg, aggravated delusions) with schizophrenia showing exacerbation within 2 months (60 days) before screening
3. Patients with a PANSS score of 4 (moderate) or higher for 2 or more of the following 5 items: delusions (P1), conceptual disorganization (P2), hallucinations (P3), suspiciousness (P6), and unusual thought content (G9)
4. Patients with a total PANSS score of 80 or higher
5. Patients who can be hospitalized from screening until the scheduled date of Visit 4
6. Patients who are aged 18 years or older at informed consent
7. Patients who are fully informed of and understand the objectives, procedures, and possible benefits and risks of the study and who voluntarily provide written consent to participate in the study. If the patient is a minor at informed consent, written consent will be obtained from a legally acceptable representative[Note] in addition to that obtained from the patient.

   Note: A legally acceptable representative is defined as a person within the second degree of kinship, in principle, who can act in the patient's best interest in the context of daily lifestyle and the existing mental relationship between the two parties.

8. Female patients, who are premenopausal and of childbearing potential, with negative pregnancy test (urine) results at screening
9. Patients who agree to practice appropriate contraception, when the patients or their partners are of childbearing potential

8.1.2 Exclusion Criteria at screening

Patients who meet any of the following criteria will be excluded from the study.

1. Patients in a coma
2. Patients under the strong influence of central nervous system depressants such as barbituric acid derivatives
3. Patients receiving treatment with adrenaline, azole antifungals (excluding drugs for external use), or human immunodeficiency virus (HIV) protease inhibitors
4. Patients with a history of or current neuroleptic malignant syndrome, tardive dyskinesia, or water intoxication
5. Patients with Parkinson's disease
6. Patients with active suicidal ideation or those with a suicide attempt history who are considered ineligible for the study by the Investigator
7. Patients with HbA1c (NGSP) of 8.4% or higher
8. Patients with physical exhaustion accompanied by conditions such as dehydration and malnutrition

9. Patients with a history of or complication(s) involving serious cardiovascular, hepatic, renal, organic brain, hematologic, endocrine, convulsive disease or other conditions, and who are considered ineligible for the study by the Investigator
10. Patients with skin injuries, skin diseases or tattoos that preclude the application of the study drug to the back, chest, or abdomen
11. Patients with a history of drug abuse, drug dependency, alcohol abuse, or alcohol dependency within 6 months (180 days) before screening
12. Patients who received any depot preparation (sustained-release formulation) of an antipsychotics within 3 months (90 days) before screening
13. Patients who received clozapine within 4 months (120 days) before screening
14. Patients who are considered resistant to treatment for psychiatric symptoms by the Investigator. Treatment resistance is defined as failure to respond to 3 or more antipsychotics within 1 year (365 days) before screening
15. Patients who previously received blonanserin
16. Patients who received monoamine oxidase (MAO) inhibitors or fluoxetine within 1 month (30 days) before screening
17. Patients who received electroconvulsive therapy within 6 months (180 days) before screening
18. Patients who are pregnant, or are nursing mothers
19. Patients with a history or complication(s) of hypersensitivity to 2 or more drugs (patients with a history or complication(s) of drug-induced allergic reactions such as anaphylaxis, rash, and urticaria)
20. Patients with a history or complication(s) of malignant tumor within 5 years before screening
21. Patients who are currently infected with HIV
22. Patients who received other investigational products or post-marketing clinical study drugs within 3 months (90 days) before screening or who have enrolled in but have not completed another clinical or post-marketing study before screening
23. Patients who are otherwise considered ineligible for the study by the Investigator

8.2 Randomization Criteria

8.2.1 Inclusion Criteria before randomization

Subjects who meet all the following criteria before randomization (at Visit 2) will be randomized.

1. Subjects with a PANSS score of 4 (moderate) or higher for 2 or more of the following 5 items: delusions (P1), conceptual disorganization (P2), hallucinations (P3), suspiciousness (P6), and unusual thought content (G9)

2. Subjects with a PANSS total score of 80 or higher

8.2.2 Exclusion Criteria before randomization

Subjects who meet any of the following criteria will be excluded from the study before randomization.

1. Subjects with a 20% or more reduction in the PANSS total score between screening and randomization (at Visit 2)

$$\left(\frac{\text{PANSS total score at screening} - \text{PANSS total score at randomization}}{\text{PANSS total score at screening} - 30} \right) \times 100 \geq 20\%$$

2. Subjects who are otherwise considered ineligible for the study by the Investigator

8.3 Criteria before the open-label treatment phase

8.3.1 Inclusion Criteria before the open-label treatment phase

Subjects who meet the following criterion will enter the open-label treatment phase.

1. Subjects who have completed the 6-week study treatment and all scheduled assessments at Visit 6 in the double-blind treatment phase, and who are considered eligible by the Investigator with no safety concerns

8.3.2 Exclusion Criteria before the open-label treatment phase

Subjects who meet any of the following criteria will be excluded from the study before the open-label treatment phase.

1. Subjects who are planning to become pregnant at any time before the end of the follow-up phase
2. Subjects who are otherwise considered ineligible for the study by the Investigator

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1 Description of Study Drug

The study drugs are shown in Table 7. The study drugs will be transdermal patches (DSP-5423P 20 mg patches, DSP-5423P 40 mg patches, and placebo patches) covered with a transparent protective liner on their adhesive side.

DSP-5423P 40 mg patches and placebo patches, which will be used in the double-blind treatment phase, are indistinguishable in color, shape, size, and packaging.

Table 7 The study drugs

Study drug	Unit dose of Blonanserin
DSP-5423P 20 mg patch	20 mg
DSP-5423P 40 mg patch	40 mg
Placebo patch	0 mg

9.2 Study Drug Packaging and Labeling

9.2.1 Package Description

Supplies will be packaged in paper boxes.

For the washout phase and the double-blind treatment phase

The study drugs for the washout phase and the double-blind treatment phase will be packaged in paper boxes with uniquely identifiable numbers, ie, a Kit ID. A paper box contains 7 plastic bags for 7-day treatments. The packaging contains 2 aluminum-laminated patches in a plastic bag (1 patch in each laminate).

For the open-label treatment phase

A paper box, with a uniquely identifiable number (a Kit ID), contains 60 aluminum-laminated study drug patches (1 patch in each laminate).

9.2.2 Labeling Description

All packaging (paper boxes, plastic bags, and aluminum laminates) for the study medications will basically be labeled with the following information and will be modified in accordance with the local regulations:

- Sponsor's name and address
- Study number (D4904020)
- Investigational New Drug statement "Clinical trial use only"
- Compound/Code or name of investigational drug (DSP-5423P)
- Lot number
- Kit ID (for paper boxes only)
- Storage conditions
- Expiration date

9.3 Study Drug Storage

All study drugs should be stored under appropriate storage conditions in a secure location to which only the Investigator and designated persons have access. The

appropriate storage condition will be specified in the guidance for drug accountability provided by the Sponsor/CRO.

9.4 Dispensing of Study Drug

The washout phase and the double-blind treatment phase

The investigator or designee will access the Interactive voice response system/ Interactive web response system(IVRS/IWRS) for dispensing the study drug to subjects at Visits 1 to 5. The IVRS/IWRS will assign a Kit ID of the study drug that is to be dispensed to the subject. The Kit ID of the study drug dispensed to the subject will be recorded in the CRFs.

The open-label treatment phase

The investigator or designee will access the IVRS/IWRS at Visit 6, Visits 101~108 (outside Japan), and Visits 101~111 (in Japan) for recording the quantity of the study drug to be dispensed to the subject.

9.5 Study Drug Accountability

<The procedure in Japan is described in the Japan Appendix.>

The Investigator or designee is responsible for storing the study drug in a secure location and for maintaining adequate records of drug disposition including the dates, quantity, and use by subjects. If the study is stopped for any reason or completed, all unused supplies of the drug will be returned to the Sponsor/CRO, unless other instructions are provided in writing by the Sponsor/CRO.

The study drug will not be dispensed to any person who is not a study subject under this protocol.

9.6 Study Drug Handling and Disposal

The Investigator or designee must on an ongoing basis maintain a drug inventory record of supplied, received, dispensed, and returned medication. The Investigator or designee is required to return all unused study drugs to the Sponsor/CRO as instructed. The Investigator or designee is required to maintain copies of medication shipping receipts (outside Japan), drug accountability records, and records of return or final disposal of the study drug.

10. TREATMENT OF SUBJECTS

The Investigator will assign a unique subject number consisting of 5 digits to each patient who provides informed consent. The subject number consists of 5 digits, which specify study center (3 digits), and patient (2 digits numbered sequentially in each study center) (eg, 10603 denotes Study center 106 and Patient 03). The subject number will be used for patient identification in all procedures throughout the study.

10.1 Study Medication

The study drug (patches) will be applied to the subject's back, chest, or abdomen once daily around the same time of the day from the beginning of the washout phase until the end of the open-label treatment phase. All patches for each day should be applied to only one location, ie, the back, the chest, or the abdomen. The study drug will be replaced every day. When the study drug patches are to be replaced, the new patches will be applied to the location different from that of the last application, or a site different from that of the last application on the same location.

The guidance for application of the study drugs

The subjects will be instructed as below:

1. The study drug will be applied directly to normal healthy skin after removing the transparent liner.
2. When the study drug patches are replaced, new patches of the study drug will be applied as soon as possible.
3. The current application site of the study drug will be protected from heat. For instance, the application site should not be warmed with a portable body warmer or hot air from a heater.
4. The current application site of the study drug will be protected from water. Before taking a bath or shower, the study drug should be removed. After taking a bath or shower, new patches of the study drug should be immediately applied to thoroughly dried skin (within approximately 1 hour after removing the previous patches).
5. The locations of previous and current applications of the study drug will be protected from light outdoors by clothing or other appropriate measures from the beginning of the washout phase until the follow-up visit.
6. No other adhesive skin patches are to be overlaid on the current application site of the study drug. No liniments should be used at the current application site of the study drug. The study drug should not be applied to any site where liniments are used.

7. Surgical tape should be used to maintain the study drug at the application site if any patches are detached or are about to become detached. When patches which have detached from the application site cannot be reapplied, no new patches will be applied until the next scheduled application.
8. The used patches will be adequately disposed to prevent anyone else from misusing them.

10.1.1 The Washout Phase

After obtaining informed consent, 2 placebo patches will be applied once daily to the eligible subjects (Section 8.1 Criteria at screening, p29) for 1 week in principle, but at least 3 days, in a single-blind manner.

10.1.2 The Double-blind Treatment Phase

DSP-5423P 40 mg patches and DSP-5423P placebo patches will be used in the double-blind treatment phase.

DSP-5423P 40 mg, 80 mg, or placebo patches will be applied once daily to the eligible subjects (Section 8.2 Randomization Criteria, p31) for 6 weeks in a double-blind manner. Table 8 shows the combinations of 2 patches in the double-blind treatment phase by treatment group.

Table 8 The study drug patches to be applied in the double-blind treatment phase

Treatment	The study drug
DSP-5423P 40 mg/day	A, P
DSP-5423P 80 mg/day	A, A
placebo	P, P

A, DSP-5423P 40 mg patch; P, DSP-5423P placebo patch

10.1.3 The Open-label Treatment Phase

DSP-5423P 20 mg patches and DSP-5423P 40 mg patches will be used in the open-label treatment phase.

One or two patches of DSP-5423P will be applied once daily to the eligible subjects (Section 8.3 Criteria before the open-label treatment phase, p32) for a further 28 weeks (outside Japan) or 52 weeks (in Japan). The initial dose of DSP-5423P in the open-label treatment phase will be 40 mg/day. After DSP-5423P 40 mg/day

application after Visit 6 until Visit 101, DSP-5423P will be applied as flexible dose within a range from 40 mg/day to 80 mg/day according to the dose adjustment criteria (Section 10.2 Dose Adjustment Criteria in the open-label treatment phase). Table 9 shows the combinations of the patches in the open-label treatment phase.

Table 9 The study drug patches to be applied in the open-label treatment phase

Treatment	The study drug	Number of patches
DSP-5423P 40 mg/day	A	1
DSP-5423P 60 mg/day	A, B	2
DSP-5423P 80 mg/day	A, A	2

A, DSP-5423P 40 mg patch; B, DSP-5423P 20 mg patch

10.2 Dose Adjustment Criteria in the open-label treatment phase

In the open-label treatment phase, the DSP-5423P dose can be increased or reduced by 20 mg/day at each adjustment within a range of 40 to 80 mg/day according to the following dose adjustment criteria.

At scheduled visit

- When the CGI-S score is between 4 and 7 and when no safety concerns arise, the DSP-5423P dose should be increased.
- When the CGI-S score is 3 or lower with no safety concerns and when the Investigator expects further efficacy of DSP-5423P, the DSP-5423P dose can be increased.

As needed

- When the Investigator considers a higher dose of DSP-5423P to be necessary due to insufficient efficacy, the DSP-5423P dose can be increased.
- When the Investigator considers a lower dose of DSP-5423P to be necessary due to the AEs, the DSP-5423P dose can be reduced.

PANSS and CGI-S should be evaluated before the dose adjustment at each unscheduled visit (Section 11.2 Efficacy Assessments, p47). DIEPSS should be evaluated as well as PANSS and CGI-S when the DSP-5423P dose is reduced due to extrapyramidal symptoms (Section11.3 Safety Assessments, p48).

After the dose adjustment, the Investigator will record the reason for the dose

adjustment in the CRFs. The DSP-5423P dose should not be changed for at least 1 week in principle, after the dose adjustment.

10.3 Concomitant Medications and Therapies

The following information on all medications used from screening until the follow-up visit will be recorded in the CRFs:

- drug name
- route
- start date
- stop date
- the reason for concomitant use
- drug category
- daily dose (for antipsychotics and antiparkinson drugs only)

For antipsychotics and antiparkinson drugs, the information on the usage for 7 days before screening will also be recorded in the CRFs.

Table 10 shows restrictions on concomitant medications/therapies from screening until the end of the follow-up phase.

Table 10 Restrictions on concomitant medications/therapies

	From screening before the washout phase	Washout phase	Double-blind treatment phase	Open-label treatment phase	Follow-up phase
Antipsychotics	B	A	A	B	C
Antimanic and antiepileptic drugs	A	A	A	B	C
MAO inhibitors	A	A	A	A	C
CYP3A4 inhibitors (External drugs for topical use can be used.)	A	A	A	A	A
CYP3A4 inducers (External drugs for topical use can be used.)	A	A	A	A	C
Adrenaline (excluding use for emergency treatment of anaphylaxis)	A	A	A	A	A
Other investigational products or post-marketed study products	A	A	A	A	A
Electroconvulsive therapy	A	A	A	A	C
Antiparkinson drugs	B	B	B	B	C
Psychotropic drugs (eg, anxiolytic drugs, antidepressants)	B	B	B	B	C
Hypnotic drugs	B	B	B	B	C
Treatments for complications	B	B	B	B	C

A, prohibited; B, restricted; C, unrestricted
Abbreviations: MAO=Monoamine oxidase; CYP3A4=Cytochrome P-450 enzyme 3A4

10.3.1 Antipsychotics

Antipsychotics except for the study drug will be restricted as follows:

- For the subjects not treated with antipsychotics at screening
  Antipsychotics will be prohibited from screening until completion of assessments at the last visit (Visit 109 outside Japan or Visit 112 in Japan) of the open-label treatment phase or the discontinuation visit. If a subject completes the double-blind treatment phase and discontinues before entering the open-label treatment phase, antipsychotics will be prohibited until completion of assessments at Visit 6.
- For the subjects treated with any antipsychotics at screening
  The antipsychotics should be tapered and completely discontinued before the beginning of the washout phase. Antipsychotics will be prohibited from the beginning of the washout phase until completion of assessments at the last visit (Visit 109 outside Japan or Visit 112 in Japan) of the open-label treatment phase or the discontinuation visit. If a subject completes the double-blind treatment phase and discontinues before entering the open-label treatment phase, antipsychotics will be prohibited until completion of assessments at Visit 6.

If urgent treatment is required because of psychiatric symptoms such as acute psychomotor excitability during the open-label treatment phase, at the discretion of the Investigator, only one antipsychotic drug excluding depot neuroleptics and blonanserin can be used concomitantly on an as-needed basis. However, all antipsychotics will be prohibited within 48 hours before the PANSS, CGI-S, and C-SSRS assessments. The total duration of concomitant use of antipsychotics for urgent treatment during the open-label treatment phase should be 5 days or less outside Japan, and 10 days or less in Japan.

10.3.2 Antimanic and Antiepileptic drugs

Antimanic and antiepileptic drugs will be prohibited from screening until completion of assessments at the last visit (Visit 109 outside Japan or Visit 112 in Japan) of the open-label treatment phase or the discontinuation visit. If a subject completes the double-blind treatment phase and discontinues before entering the open-label treatment phase, antimanic and antiepileptic drugs will be prohibited until completion of assessments at Visit 6. When psychiatric symptoms worsen during the open-label treatment phase, antimanic and antiepileptic drugs may be used. If the psychiatric symptoms improve, antimanic and antiepileptic drugs may be tapered or discontinued.

10.3.3 Other Prohibited Medications

The concomitant use of the following drugs, food, and beverages will be prohibited from screening until completion of assessments at the last visit (Visit 109 outside Japan or Visit 112 in Japan) of the open-label treatment phase or the discontinuation visit. If a subject completes the double-blind treatment phase and discontinues before entering the open-label treatment phase, the concomitant use of the following drugs, food, and beverages will be prohibited until completion of assessments at Visit 6.

- Monoamine oxidase (MAO) inhibitors
- Cytochrome P-450 enzyme 3A4 (CYP3A4) inducers (eg, phenytoin, carbamazepine, rifampin, Saint-John's wort). External drugs for topical use can be used with no restrictions.
- CYP3A4 inhibitors (eg, itraconazole, fluconazole, erythromycin, foods and beverages containing grapefruit). External drugs for topical use can be used with no restrictions.
- Adrenaline (excluding use for emergency treatment of anaphylaxis)
- Other investigational products or post-marketing clinical study products

CYP3A4 inhibitors, adrenaline (excluding use for emergency treatment of anaphylaxis), other investigational products and post-marketing clinical study products will also be prohibited until the follow-up visit.

10.3.4 Prohibited Therapies

Electroconvulsive therapy will be prohibited from screening until completion of assessments at the last visit (Visit 109 outside Japan or Visit 112 in Japan) of the open-label treatment phase or the discontinuation visit. If a subject completes the double-blind treatment phase and discontinues before entering the open-label treatment phase, electroconvulsive therapy will be prohibited until completion of assessments at Visit 6.

10.3.5 Restricted Medications

10.3.5.1 Antiparkinson drugs

Antiparkinson drugs will be restricted as follows:

(1) From screening until the end of the double-blind treatment phase

- For the subjects not treated with antiparkinson drugs at screening
  Antiparkinson drugs will be prohibited from screening until completion of DIEPSS assessments at Visit 6 or the discontinuation visit.
- For the subjects treated with antiparkinson drugs at screening
  Antiparkinson drugs will be tapered and completely discontinued before beginning of the washout phase. Antiparkinson drugs will be prohibited from the beginning of the washout phase until completion of DIEPSS assessments at Visit 6 or the discontinuation visit.

If extrapyramidal symptoms occur or worsen during the washout phase or double-blind treatment phase, only one of the antiparkinson drugs listed in Table 11 may be used and the dose may not exceed the maximum daily dose. If the antiparkinson drug is not effective, the drug may be swiched to another antiparkinson drug listed in Table 11. If the drugs listed in Table 11 are not available outside Japan, another similar drug at an equivalent dose will be permitted with prior authorization of the medical monitor (Table 1 Emergency Contact Information for outside Japan, p3). If the extrapyramidal symptoms improve, antiparkinson drugs may be tapered or discontinued.

Table 11 Permitted concomitant antiparkinson drugs

Antiparkinson drug	Maximum dose
Benztropine	6 mg/day
Biperiden	6 mg/day
Promethazine	200 mg/day
Trihexyphenidyl	10 mg/day

(2) During the open-label treatment phase

For the subjects treated with an antiparkinson drug at the end of the double-blind treatment phase (Visit 6), the antiparkinson drug may be continued with no dosage modification.

If extrapyramidal symptoms occur or worsen, antiparkinson drugs may be used. While the drugs listed in Table 11 are recommended, other antiparkinson drugs will be permitted. If the extrapyramidal symptoms improve, antiparkinson drugs may be tapered or discontinued.

10.3.5.2 Psychotropic drugs

Psychotropics (eg, anxiolytics, antidepressants) for psychiatric symptoms such as anxiety and agitation will be restricted as follows:

(1) From screening until the end of the double-blind treatment phase

Psychotropics will be prohibited from screening until completion of assessments at Visit 6 or the discontinuation visit.

When psychiatric symptoms, such as anxiety, agitation and irritation, occur, lorazepam may be used as needed at 3 mg/day or less. If lorazepam is not available outside Japan, another similar drug at an equivalent dose may be used with prior authorization of the medical monitor (Table 1 Emergency Contact Information for outside Japan, p3).

However, all psychotropics will be prohibited within 12 hours before assessments of the PANSS, CGI-S, and C-SSRS.

Table 12 Permitted concomitant psychotropic drug

Lorazepam	Maximum dose, 3 mg/day

(2) During the open-label treatment phase

When psychiatric symptoms, such as anxiety, agitation and irritation, occur, benzodiazepine receptor agonists (eg, lorazepam) may be used.

However, all psychotropics will be prohibited within 12 hours before assessments of the PANSS, CGI-S, and C-SSRS.

10.3.5.3 Hypnotic drugs

Hypnotic drugs will be restricted as follows:

(1) From screening until the end of the double-blind treatment phase

Hypnotic drugs will be prohibited from screening until completion of assessments at Visit 6 or the discontinuation visit.

If insomnia occurs or worsens, only one of the hypnotic drugs listed in Table 13 may be used and the dose may not exceed the maximum daily dose. If the hypnotic drug is not effective, the drug may be switched to another hypnotic drug listed in Table 13. If the drugs listed in Table 13 are not available outside Japan, another similar drug at an equivalent dose will be permitted with prior authorization of the medical monitor (Table 1 Emergency Contact Information for outside Japan, p3).

However, all hypnotic drugs will be prohibited within 12 hours before assessments of the PANSS, CGI-S, and C-SSRS. If the insomnia improves, hypnotic drugs may be tapered or discontinued.

Table 13 Permitted concomitant hypnotic drugs

Hypnotic drugs	Maximum dose
Brotizolam	0.25 mg/day
Eszopiclone	for subjects under age 65 years, 3 mg/day for subjects 65 years or older, 2 mg/day
Lormetazepam	2 mg/day
Rilmazafone	2 mg /day
Triazolam	0.25 mg/day
Zolpidem	10 mg/day
Zopiclone	10 mg/day

(2) During the open-label treatment phase

For the subjects treated with a hypnotic drug at the end of the double-blind treatment phase (Visit 6), the hypnotic drug may be continued with no dosage modification. When insomnia occurs or worsens, the hypnotic drugs listed in Table 13 or benzodiazepine receptor agonists may be used.

However, all hypnotic drugs will be prohibited within 12 hours before assessments of the PANSS, CGI-S, and C-SSRS. If the insomnia improves, hypnotic drugs may be tapered or discontinued.

10.3.6 Medications for complications

All drugs used for the treatment for complications (eg, hypertension, hyperlipidemia, diabetes) at screening should be continued without any dosage modification from screening until the last visit (Visit 109 outside Japan or Visit 112 in Japan) of the open-label treatment phase or the discontinuation visit. If a subject completes the double-blind treatment phase and discontinues before entering the open-label treatment phase, any dose modification of the concomitant drugs will be prohibited until completion of assessments at Visit 6. If the complications worsen or improve, the dosage of the concomitant drugs for these complications may be changed accordingly.

10.4 Inpatient or Outpatient

All subjects will be hospitalized from screening until Day 14 (Visit 4) in the double-blind treatment phase. After Day 14 and completion of assessments at Visit 4, any subject who meets all the following criteria can be an outpatient.

- The subject has family members or care-givers (eg, a social worker, case worker, nurse) who can aid in applying the study drug to the subject and visit the study center.
- The Investigator considers the subject, whose psychiatric symptoms are stable without safety concerns, can be an outpatient.

During the inpatient/hospitalized period in the double-blind treatment phase, all subjects will be permitted to stay outside of the study center only twice, for 3 days and 2 nights each time, as needed. The subject who are currently hospitalized must return to the study center the day before each scheduled visit. All subjects can be discharged from the study center after the treatment in the double-blind treatment phase and completion of assessments at Visit 6, or after completion of assessments at the discontinuation visit. In the open-label treatment phase, the subjects can be

inpatients or outpatients.

The Investigator will record the dates of hospitalization and discharge in the CRFs.

10.5 Contraception Requirements

Subjects who are of childbearing potential, and whose partners are of childbearing potential must practice adequate contraception from informed consent until the follow-up visit. Adequate contraception is defined as continuous use of a barrier method (eg, condoms, diaphragms and intrauterine contraceptive device or system), a hormonal contraceptive, or abstinence.

10.6 Treatment Compliance

The Investigator will instruct subjects that the subjects will return any unused study drugs at each visit. The Investigator will monitor the treatment compliance at each visit.

The Investigator will record the dates of the initial and final applications, the date of the final removal of the study drug, and the number of applied patches during the washout phase and the double-blind treatment phase in the CRFs.

The Investigator will record the dates of the initial and final applications and the number of applied patches for each dose during the open-label treatment phase, and the date of final removal of the study drug.

10.7 Treatment Assignment and Blinding

10.7.1 Treatment Assignment

Subjects, who will be eligible at Visit 2, will be randomly assigned to receive one of the following three treatments in a double-blind fashion (1:1:1) by a Kit ID obtained from the IVRS/IWRS.

- DSP-5423P 40 mg/day
- DSP-5423P 80 mg/day
- Placebo

In the subsequent visits (Visit 3, 4 and 5), the Kit ID will be allocated to a subject to a particular treatment group through IVRS/IWRS. The Kit ID identifies the subject for data collection purpose and not be reused.

10.7.2 Blinding

This study will contain the double-blind treatment phase. The subjects, Investigators, staff of the study centers, persons performing the assessments, clinical operations personnel, data analysts, personnel at central laboratories, the central ECG reader, and the principal ECG analyst will remain blinded to the identity of the treatment from randomization until the database lock and unblinding for the double-blind treatment phase, as follows:

- The randomization code will be kept strictly confidential until the unblinding, and will not be accessible by anyone except for the personnel performing the pharmacokinetic analysis and an appointed independent biostatistician and programmer(s) performing the interim analysis (see Section 15.4.3 Confidentiality of Interim Data and Analyses, p72) .
- In the double-blind treatment phase, the study drugs will be identical in packaging, labeling, and appearance.
- PANSS and CGI-S at Week 6 will be evaluated before the beginning of the open-label treatment phase. The data will be recorded in the CRFs before the initial assessments in the open-label treatment phase (Open-Week 1 [Week 7]). PANSS and CGI-S data from screening to Week 6 recorded in the CRFs may only be revised if there is a valid reason (eg, incorrect input).
- Serum prolactin concentrations measured from screening until the end of the double-blind treatment phase will not be disclosed before all other data from the double-blind treatment phase have been locked.
- Plasma concentrations of blonanserin and its metabolite M-1 will not be disclosed before the database lock and the unblinding of the double-blind treatment phase.

10.8 Emergency Unblinding Procedures

In the case of medical emergencies when the Principal Investigator or the authorized delegate needs to know what study treatment has been applied to a subject to ensure the subject's safety, he or she should contact the Sponsor, the designee or the medical monitor about the unblinding (Table 1 and Table 2 Emergency Contact Information, p3). If possible, the reason for or the necessity of the unblinding should be discussed before unblinding.

A 24-hour code-break service will be available via the IVRS/IWRS for the Principal Investigator. All treatment code breaks must be fully documented and signed with the time, date, reason, and name of the person responsible for breaking the code and

tracked on the unblinding log. The unblinding must result in the withdrawal of the subject from the study, and the subject should return to the study center and complete the discontinuation assessments within 5 days of the drug application last study.

The Sponsor will retain the right to break the randomization code for a subject who develops any serious adverse events (SAEs) that are unexpected and are suspected to be causally related to the study drug, and that potentially require expedited reporting to regulatory authorities. The randomization codes will not be broken for the planned analyses of the double-blind treatment phase until all data excluding prolactin concentrations in the double-blind treatment phase will be locked, except the randomization codes will be revealed to the independent biostatistician and the programmer(s) performing the interim analysis.

11. STUDY ASSESSMENTS

A study schematic is presented in Figure 1. A summary of assessments to be conducted at each visit is presented in Table 3 to 5 Schedule of Assessments (p10~p13). Assessments will be conducted within the time frames specified. Day 1 is defined as the day of the initial application of the study drug in the double-blind treatment phase. Open-Day 1 is also defined as the day of the initial application of the study drug in the open-label treatment phase.

Laboratory findings and results of the study assessments will be recorded in source documents. The following data will be recorded in the CRFs.

11.1 Demographics and Baseline Characteristics

Demographics:

Ethnicity, race, sex, date of birth, height, body weight, inpatient/outpatient status at informed consent, and duration of hospitalization at informed consent

Disease information:

Time of the first onset of schizophrenia, the number of previous episodes of schizophrenia, time of onset of the current episode, and complications

11.2 Efficacy Assessments

The concomitant use of medications is restricted, as described in Section 10.3 Concomitant Medications and Therapies (p38). When the efficacy assessments are conducted, the concomitant use of restricted medications will be recorded in the CRFs.

11.2.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS[ref.11] is an interview-based measure of the severity of psychopathology in adults with psychotic disorders.

A person, who will be a certified rater for PANSS assessments, will receive specific training and education for the PANSS assessment provided by the Sponsor/CRO and will be certified by the Sponsor/CRO before his/her initial assessment of PANSS. The certified rater will rate 30 items on a 7-point scale of 1 to 7. Dates of the assessments and the results will be recorded in the CRFs.

When the study treatment is completed or prematurely discontinued, PANSS will be rated before the first post-treatment with other antipsychotics. When the DSP-5423P dose is changed at an unscheduled visit in the open-label treatment phase, PANSS will be rated before dose adjustment.

11.2.2 Clinical Global Impressions scale-Severity of illness (CGI-S)

CGI-S [ref.12] is a research rating tool of the subject's current disease state on a 7-point scale of 1 to 7. The Investigators will receive specific training before their initial assessment of CGI-S. Dates of the assessments and the results will be recorded in the CRFs.

When the study treatment is completed or prematurely discontinued, CGI-S will be rated before the first post-treatment with other antipsychotics. When the DSP-5423P dose is changed at an unscheduled visit in the open-label treatment phase, CGI-S will be rated before dose adjustment.

11.3 Safety Assessments

11.3.1 Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Section 12 SAFETY REPORTING (p52).

AEs and SAEs will be monitored throughout the study at all visits including telephone assessments.

11.3.2 Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS)

The DIEPSS[ref.13] is a rating tool of extrapyramidal symptoms induced by

antipsychotics and consists of 8 individual items; gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, and dyskinesia; and one global assessment; overall severity. The severity of each item is on a 5-point scale of 0 to 4. Dates of the assessments and the results will be recorded in the CRFs.

If the DSP-5423P dose is reduced due to extrapyramidal symptoms at an unscheduled visit in the open-label treatment phase, DIEPSS will be assessed before dose reduction.

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

The C-SSRS [ref.14] is a rating tool designed to systematically assess and track suicidal behavior and suicidal ideation throughout the study. The C-SSRS can comprehensively identify suicidal events and limit the over-identification of suicidal behavior.

The Investigators will receive specific training before their initial assessment of C-SSRS. Date of the assessments and the results will be recorded in the CRFs.

11.3.4 Skin Irritation Assessment

The Investigator will evaluate any skin reactions at the application sites according to the Table 14 and record the score in the CRFs. If more than one skin reaction from +− to ++++ is observed at the application sites, the stronger reaction will be scored and recorded in the CRFs.

Table 14 Scoring of Skin Reactions[ref.15]

Skin reactions	Score
Negative	−
Faint erythema	+−
Erythema	+
Erythema + Edema	++
Erythema + Edema + Papules, Serous papules, Vesicles	+++
Coalescing vesicles	++++

11.3.5 Clinical Laboratory Tests

Blood and urine samples will be collected for clinical laboratory tests. The Investigators will record the date of collection and whether or not the subject is under

fasting conditions (at least 10 hours after the last meal) in the CRFs. All clinical laboratory tests will be performed centrally.

The clinical laboratory tests required by the protocol are listed in Table 15. Detailed instructions regarding clinical laboratory procedures, sampling, shipping, and reporting can refer to the instructions manual provided by the Sponsor/CRO.

Guidance for Blood sample Collection

- From screening until the end of the double-blind treatment phase
  Blood samples will be collected under fasting conditions (at least 10 hours after the last meal).
- During the open-label treatment phase
  Blood samples will be collected under fasting conditions (at least 10 hours after the last meal) at the last visit (Visit 109 outside Japan or Visit 112 in Japan). At other visits, blood samples should be collected under fasting conditions, whenever possible.
- At the discontinuation visit
  Blood samples will be collected under fasting conditions (at least 10 hours after the last meal).

Table 15 Contents of laboratory variables

Hematology	white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, differential white blood cell count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
Blood biochemistry	total protein, total bilirubin, AST, ALT, ALP, γ-GTP, LDH, total cholesterol, triglycerides, BUN, creatinine, CK, Na, K, Cl, blood glucose, HbA1c, serum prolactin*
Urinalysis (Qualitative)	glucose, protein, occult blood, urobilinogen
Pregnancy test (premenopausal women of childbearing potential only)	urine chorionic gonadotropin

* Serum prolactin concentrations measured from screening until the end of the double-blind treatment phase will not be disclosed until the other data of the double-blind treatment phase have been locked.

11.3.6 Vital Signs and Body Weight

Systolic and diastolic blood pressures (sitting), pulse rate, body temperature (axilla), and body weight will be measured. Dates of measurements and the results will be

recorded in the CRFs.

11.3.7 12-lead ECGs

The Investigator will perform 12-lead ECG at rest and record the dates and times of assessments in the CRFs. The Investigator will retain ECG tracings and send them electronically to the central ECG reader. The central ECG reader will analyze ECG tracings and calculate the following ECG parameters: RR interval, QT interval, PR interval, QRS interval, and QTc interval (QTc Fridericia [QTcF] and QTc Bazett [QTcB]). The central ECG reader will report analysis results and ECG parameters to the Sponsor and the Investigator.

The principal ECG analyst will comprehensively evaluate the effect of study treatment on QTc prolongation.

11.4 Pharmacokinetic Assessments

Measurement

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

Recording

The following information will be recorded in the CRFs:

- Dates and times of blood sample collection
- Dates and times of the last two applications of DSP-5423P before blood sample collection
- Locations for the last two applications of DSP-5423P before blood sample collection
- DSP-5423P doses of the last two applications before blood sample collection (in the open-label treatment phase only)

Timing and volume of blood collection

Six milliliters of blood will be collected at each time point shown in Table 3 to 5 Schedule of Assessments.

Processing of blood collection

Blood samples will be collected into heparinized (heparin sodium) blood collection tubes and should be stored in ice before being centrifuged (4°C, 3000 rpm [approximately 1700 g], 10 minutes). The entire volume of plasma will be placed in a container and stored in a freezer (set at −20°C or lower).

When a centrifuge with cooling system is not available, ice chilled blood samples should be centrifuged (at room temperature, 3000 rpm [approximately 1700 g], 10 minutes) as immediately as possible. The entire volume of plasma should be also placed in a container as immediately as possible and will be stored in a freezer (set at −20°C or lower).

Shipment of specimens

All specimens for drug concentration measurements will be collected by the clinical laboratory and shipped to the bioanalysis laboratory.

Measurements and Reporting

The bioanalysis laboratory will measure the plasma concentrations of blonanserin and its metabolite M-1 and prepare a bioanalysis report. Results obtained in the double-blind treatment phase will be reported to the Sponsor after unblinding.

12. SAFETY REPORTING

12.1 Definitions

12.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a study subject administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from the beginning of the study treatment in the washout phase until the follow-up visit. AEs also include other untoward events occurring from the beginning of the study treatment in the washout phase until the follow-up visit, for instance, events occurring in association with study-related procedures or assessments, or those occurring under placebo treatment.

AEs that occur during the washout phase and worsen during the double-blind treatment phase will be recorded as AEs in the washout phase and also as AEs in the double-blind treatment phase. AEs that occur during the washout phase and worsen during the open-label treatment phase will be recorded as AEs in the washout phase and also as AEs in the open-label treatment phase. The date of worsening will be

recorded as the onset date of the worsening AE. Likewise, AEs that occur during the double-blind treatment phase and worsen during the open-label treatment phase will be recorded as AEs in the double-blind treatment phase and also as AEs in the open-label treatment phase, with the date of worsening as the onset date. In addition, AEs that occur during the washout phase or double-blind treatment phase without further worsening in the following phase will be recorded as AEs in the washout phase or a AEs in the double-blind treatment phase, respectively.

Lack of efficacy may be an expected potential outcome and should not be reported as an AE unless the event is unusual in some way. New signs and symptoms of the underlying disease, or signs and symptoms of an emerging disease should be recorded as AEs.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be recorded as the AE and not the individual signs/symptoms.

12.1.2 Serious Adverse Events

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening (ie, a subject is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death).
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.3 Collection and Recording Adverse Events, p54); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that

pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

12.2 Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs. When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by the Investigator. The Investigator must determine the clinical significance of all out of range values. Clinical laboratory test with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator. Laboratory reports will be initialed and dated by the Investigator.

All ECG tracings at the study center and ECG over-read reports by the central ECG reader will be reviewed by the Investigator. The Investigator must determine the clinical significance of all abnormal ECGs. An ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings will be initialed and dated by the Investigator.

12.3 Collection and Recording Adverse Events

All AEs will be, in principle, followed up until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up. All AEs must be collected and recorded in the subject’s study records/source documents, in accordance with the Investigator’s normal clinical practice. AEs will be recorded in the CRFs

from the beginning of the study treatment in the washout phase until the follow-up visit.

Each AE is to be evaluated for duration, severity, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. If any AEs related to skin disorders occur at the application site, the Investigator will record the location (the back, chest or abdomen) of AEs occurrence.

Definitions for severity, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

- Mild – Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- Moderate – Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- Severe – Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The action taken with the study treatment:

During the washout phase

- Drug Withdrawn – Study drug stopped permanently.
- Dose Not Changed.
- Not Applicable.

During the double-blind treatment phase

- Drug Withdrawn – Study drug stopped permanently.
- Dose Not Changed.
- Not Applicable.

During the open-label treatment phase

- Drug Withdrawn – Study drug stopped permanently.
- Dose Reduced.
- Dose Increased.
- Dose Not Changed.
- Not Applicable.

The outcome of the AE:

- Recovered/Resolved.
- Recovering/Resolving.
- Not Recovered/Not Resolved.
- Recovered/Resolved with Sequelae.
- Fatal.
- Unknown.

The causal relationship of the AE to the study treatment:

Not related

- Not related – Improbable temporal relationship and is plausibly related to other drugs or underlying disease.

Related

- Possible – occurred in a reasonable time after study drug administration (application), but could be related to concurrent drugs or underlying disease.
- Probable – occurred in a reasonable time after study drug administration (application), is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
- Definite – occurred in a reasonable time after study drug administration (application) and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person outside Japan for protocol related questions or discussion of AEs. In Japan, the Sponsor or the designees are the contact persons. The contact information as well as other emergency contact information can be found in Table 1 and 2 Emergency Contact Information (p3).

12.4 Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor/CRO:

- SAE
- Pregnancy

Emergency contact information can be found in Table 1 and 2 Emergency Contact Information (p3).

12.4.1 Serious Adverse Event

If the Investigator or staff of study centers becomes aware of SAE that occurs in a

study subject from the beginning of the study treatment in the washout phase until the follow-up visit, this must be reported immediately to the Sponsor/CRO whether considered related or unrelated to the study drug. SAEs occurring from the beginning of the study treatment in the washout phase until the follow-up visit must be recorded in the CRFs.

Following the end of subject participation in the study, the Investigator should report SAEs "spontaneously" to the Sponsor/CRO if considered at least possibly related to the study drug.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

The Investigator must inform the Sponsor/CRO (Table 1 and 2 Emergency Contact Information) of any SAEs that occur during the course of the study within 24 hours of the Investigator becoming aware of the SAE.

The SAE report should include the following information:

1. Study number (D4904020)
2. Subject number
3. Sex
4. Date of birth
5. Name of investigator and study site
6. Nature of SAE
7. Criterion for classification as "serious"
8. Date of initial administration of the study drug
9. Start date of SAE
10. Causality (if sufficient information is available to make this classification)
11. History of any ADRs
12. Relevant special conditions of the subject
13. History of the current disease and treatment for the disease
14. Details of the SAE
15. Treatment for the SAE
16. Details of study treatments
17. Details of concomitant medications
18. Details on course of the SAE
19. If the subject died, date of death, cause of death, relationship between the SAE

and death, anatomic findings (if available)

As a minimum requirement for the first report, information on items 1 to 10 described above should be provided directly or in a form of a report, by facsimile, or by telephone. The Principal Investigator should report available information in writing within 7 calendar days after the first reporting (this procedure is not mandatory in the case that the Principal Investigator has already submitted the first report, including all necessary information listed above). The Principal Investigator should report other necessary information not included in the first and second reports in writing as it becomes available. The Sponsor/CRO may request additional information, if deemed necessary.

The Sponsor or designee will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB)/IEC by the Principal Investigator or the appropriate person at the study center. In Japan, these SAEs must be promptly reported in writing to the head of the study center by the Principal Investigator.

12.4.2 Pregnancy

Pregnancies that occur from the beginning of the study treatment in the washout phase until the follow-up visit will be collected and reported to the Sponsor/CRO.

If a subject becomes pregnant from the beginning of the study treatment in the washout phase until the follow-up visit, she will be instructed to commence discontinuation of the study medication. Further, the subject (or female partner of a male subject) will be instructed to return promptly after the first notification of pregnancy to the study center and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the subject will no longer receive any additional study medication. All pregnancies will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).
If the Investigator becomes aware of pregnancies, this must be promptly reported directly or by telephone or facsimile to the Sponsor/CRO (Table 1 and 2 Emergency Contact Information). The Investigator must complete the Pregnancy Event Form and send it to the Sponsor/CRO.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs

were detected.

13. TERMINATION OF SUBJECT FROM STUDY/DISCONTINUATION OF STUDY DRUG

13.1 Criteria for Subject Termination

Subjects may terminate the study participation at any time for any reason.

The possible reasons for the termination of study participation are as follows:

- Adverse event
- Suicide ideation
- Study drug discontinuation
- Lack of efficacy
- Lost to follow-up
- Pregnancy
- Withdrawal by subject
- Failure to apply >50% of the study medication since the last visit
- Protocol violation
- Other

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE or suicide ideation, becomes pregnant), or discontinuation of the study drug should be considered, the subject must be discontinued from the study treatment.

The date of discontinuation and the reason for discontinuation will be recorded in the appropriate CRF. Subjects who prematurely terminate the study participation will not be replaced.

13.2 Clinical Assessments after Study Drug Discontinuation

Every effort should be made for all randomized subjects prematurely discontinuing the study drug, regardless of cause, to undergo final evaluation procedures, in accordance with the discontinuation visit and the follow-up visit as described in Table 4 Schedule of Assessments for outside Japan (p11) or Table 5 Schedule of Assessments for Japan (p13). The subject will undergo the discontinuation assessments within 5 days of the last study drug application. However, if a subject completes the double-blind treatment

phase and discontinues before entering the open-label treatment phase, the subject will undergo the follow-up visit in Table 4 or that in Table 5.

Subjects with study drug application during the washout phase and prematurely discontinuing before randomization, 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 4 Schedule of Assessments for outside Japan (p11) or Table 5 Schedule of Assessments for Japan (p13).

13.3 Early Termination of the Study for Futility

If the Sponsor decides early termination of the study for futility on the basis of the interim analysis, Investigators must stop obtaining consent from any new subjects and stop enrolling any subjects into the study. Investigators will inform all subjects already enrolled about the study termination. All subjects must be discontinued from the study treatment at any time during the course of the study and will undergo the clinical assessments described in Section13.2 Clinical Assessments after Study Drug Discontinuation.

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at multiple study centers for safety or administrative reasons at any time while ensuring that early termination does not compromise the safety or well-being of the subjects. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the study center closed for whatever reason, study medications pertaining to the study must be returned to the Sponsor/CRO.

If the Sponsor decides to prematurely terminate the study, the Sponsor will inform the Investigator and regulatory authorities of this termination and its reason, and in addition, the head of the study center in Japan must be informed. In the event of study or study center termination, the subjects will be provided with access to standard care.

15. STATISTICS

A statistical analysis plan (SAP) will provide details on the statistical analysis method planned for the study. The SAP will be finalized before unblinding. Unblinding and data analysis for the double-blind treatment phase will occur after all subjects have completed or discontinued the double-blind treatment phase, the database for the double-blind treatment phase has been finalized, and the analysis populations other than the open-label population have been determined. The analysis for the entire duration of the study will be conducted at the time of regulatory submission as well as after the study completion. For the analysis for the entire duration of the study, we will combine data from databases for both double-blind phase and open-label phase.

For the analysis of pharmacokinetics (PK) or pharmacokinetics-pharmacodynamics (PK-PD) not defined in the protocol, detailed procedures will be described in PK or PK-PD analysis plan. If necessary, PK or PK-PD data will be combined with those of other studies and analyzed. Results will be reported separately from the clinical study report.

In the current study, the unblinded interim analysis for futility will be performed (Section15.4 Interim Analysis, p70). The interim analysis plan describing further detail of interim analysis will be finalized before performing of the interim analysis, separately from the SAP. When the study is continued, the analyses will be performed as per the protocol and the SAP. When the study is early terminated after the interim analysis, the final analysis will be performed.

15.1 Sample Size Determination

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

Rationale

The sample size for the study has already been determined by a Monte-Carlo simulation using Statistical Analysis Software (SAS Version 9.3, SAS Institute). The sample size calculation is based on the number of subjects required for the primary analysis in the modified intention-to-treat (mITT) population, wherein 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 for the multiplicity adjustment to the multiple comparisons between each DSP-5423P (40 and 80 mg/day) group and the placebo group. Neither a placebo-controlled study nor an active-controlled study of DSP-5423P has been conducted. In contrast, a double-blind placebo-controlled study of DSP-5423 (tablets, 2.5, 5 and 10 mg/day) treatment for 6 weeks for comparison with the placebo has been conducted[ref.16]. The results of the study are shown in Table 16. The sample size for the study has been determined on the basis of the effect size estimated using the result of each DSP-5423 group except DSP-5423 2.5 mg/day in this study because DSP-5423P doses in the study were chosen to correspond to DSP-5423 8 and 16 mg/day.

Table 16 Change in PANSS total score

Treatment group	N	Change in PANSS total score from baseline	
		Mean ± SD	Effect Size (95% CI)
DSP-5423 2.5 mg	60	-20.433±21.101	-0.338 (-0.689, 0.021)
DSP-5423 5 mg	57	-27.123±17.461	-0.650 (-1.020, -0.279)
DSP-5423 10 mg	62	-29.516±24.721	-0.667 (-1.030, -0.304)
HPD 10 mg	58	-27.569±17.623	-0.669 (-1.038, -0.299)
Placebo	61	-12.213±26.840	-

Abbreviation: HPD=haloperidol

The effect size[ref.17] was estimated to be 0.650 for DSP-5423 5 mg/day and 0.667 for DSP-5423 10 mg/day based on this study. It is considered that the change in PANSS total score from baseline will be smaller than in past study because in the earlier study, in which the enrollment criteria targeted outpatients or inpatients hospitalized within two weeks according to acute aggravation, more patients with a newly exacerbated psychotic state were enrolled than in this study. In addition, a trend for drug-placebo differences in the clinical trial to be diminishing annually in the field of schizophrenia has been pointed out[ref. 18]. For the reasons noted above, the effect size in the present 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 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.

15.2 Analysis Populations

The primary efficacy analysis will be performed in the modified intention-to-treat (mITT) population. The efficacy analysis on the primary variable will also be performed in the per-protocol (PP) population for sensitivity analysis. Some efficacy data in the open-label treatment phase will be analyzed for the open-label treatment phase population. The safety analysis will be performed in the safety population. Efficacy and safety analyses for DSP-5423P treatment period will be performed on DSP-5423P dosed population. The mITT analysis will be performed using the assigned treatment groups, and the safety analysis using the groups of the treatment actually received.

15.2.1 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.

15.2.2 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

15.2.3 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.

15.2.4 Safety population

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

15.2.5 DSP-5423P dosed population

The DSP-5423P dosed population will consist of all subjects who apply DSP-5423P at least once during the study.

15.2.6 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

15.3 Data Analysis

15.3.1 Subject Disposition

The number of subjects who provide informed consent, enroll in the wash-out phase, are randomized, not apply the study drug in the double-blind treatment phase, apply the study drug in the double-blind treatment phase and complete or discontinue the double-blind treatment phase will be presented by treatment group.

Also, the number of subjects who complete the double blind treatment phase, discontinue the open-label treatment phase before the initial application in the open-label treatment phase, apply DSP-5423P in the open-label treatment phase at least once, and complete or discontinue the open-label treatment phase will be presented both overall and by treatment group.

15.3.2 Drug Exposure and Compliance

15.3.2.1 Double-blind treatment phase

Duration of treatment and compliance with the study drug in the double-blind treatment phase will be summarized by treatment group for all of the analysis populations.

15.3.2.2 Open-label treatment phase

Duration of treatment, mean, modal, and last daily dose, and compliance with DSP-5423P in the open-label treatment phase will be summarized both overall and by treatment group for all of the analysis populations.

15.3.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) will be identified by a blinded data review before unblinding. IPDs will be presented in the data listing.

15.3.4 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized both overall and by treatment group for all of the analysis populations.

15.3.5 Efficacy Analysis

15.3.5.1 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}: $\mu_{80} \neq \mu_{placebo}$.

15.3.5.2 Primary analysis

The primary efficacy variable is the change in PANSS total score from baseline at Week 6 for testing the superiority of DSP-5423P (40 or 80 mg/day) to placebo. A mixed model for repeated measurements (MMRM) method will be used in 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. 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 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 above three covariance structures, the first covariance 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.

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 in the PP population to obtain additional information on the robustness of the results.

15.3.5.3 Secondary Efficacy Endpoint Analysis

15.3.5.3.1 Double-blind treatment phase

1. Change in PANSS subscale scores from baseline at Week 6
2. Change in PANSS five-factor model scores from baseline at Week 6
3. Change in CGI-S score from baseline at Week 6
4. Proportion of subjects who achieve a response, defined as 20% or greater improvement from baseline in PANSS total score 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. 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. The secondary variable (4) will be analyzed using a logistic regression model, which will include baseline PANSS total score, pooled study center, and treatment.

15.3.5.3.2 Open-label treatment phase

The time to treatment discontinuation from the initial application in the open-label treatment phase will be analyzed using the Kaplan-Meier method for the open-label population. The Kaplan-Meier curves will be shown overall and by treatment group in the double-blind treatment phase.

15.3.5.3.3 DSP-5423P Treatment Period

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

Summary statistics for the secondary variables (1) to (4) will be provided for each visit and LOCF endpoint by treatment group for the DSP-5423P dosed population.

15.3.5.4 Adjustment for Multiplicity

The Hochberg procedure will be used to control the overall Type I error at 5% by taking into account multiple dose regimens for the primary efficacy analysis.
The interim analysis for futility does not inflate the overall Type 1 error as the significance level of the final analysis will not be accounted for the futility stopping [ref.19,20].

15.3.5.5 Subgroup Analysis

Subgroup analysis will be performed for the change in PANSS total score and CGI-S score from baseline at Week 6. The subgroup analysis will include sex and age. Inferential analysis of treatment-by-subgroup interaction at Week 6 will be performed for each subgroup variable using the MMRM method on the mITT population. The model will include treatment, visit, baseline data, pooled study center, subgroup, treatment-by-subgroup, treatment-by-visit, visit-by-subgroup, and treatment-by-subgroup-by-visit interactions.

15.3.6 Safety Analysis

15.3.6.1 Adverse Events

The summary of AEs will be limited to treatment-emergent AEs (TEAEs), which are defined as AEs with onset on or after Day 1. An ADR will be defined as an AE related to the study treatment; an AE of which causality with study drug is related, probably related, or possibly related.

The number and percentage of subjects with at least one AE or ADR in the double-blind treatment phase for each preferred term and system organ class will be summarized by treatment group. Also, the number and percentage of subjects with at least one AE or ADR developing after applying DSP-5423P during the entire study duration will be summarized overall and by treatment group. This summary will be repeated for death, SAEs, AEs leading to study discontinuation, severe AEs, extrapyramidal AEs, and skin-related AEs at the application site.

15.3.6.2 DIEPSS

1. Change in DIEPSS total score (excluding overall severity) from baseline at

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

The safety variables (1) will be analyzed using the MMRM method and the LOCF ANCOVA described above for the primary efficacy variable.
Summary statistics for the safety variables (2), (3) and (4) will be provided for each visit and LOCF endpoint by treatment group.

15.3.6.3 C-SSRS

The numbers and percentages of subjects with suicidal ideation and suicidal behavior will be summarized by treatment group.

15.3.6.4 Skin irritation assessment

The distribution of the worst score in the skin irritation assessment for each subject during the double-blind treatment phase, and the DSP-5423P treatment period will be shown.

15.3.6.5 Laboratory tests, vital signs, body weight, and 12-lead ECG

Summary statistics for laboratory tests, vital signs, body weights, and 12-lead ECG parameters will be provided at each visit by treatment group.

15.3.6.6 Concomitant Medications

The number and percentage of subjects with concomitant use of antiparkinson drugs in the double-blind treatment phase will be summarized by treatment group. The number and percentage of subjects with concomitant use of antiparkinson drugs for the DSP-5423P treatment period will be summarized overall and by treatment group.

15.3.6.7 Subgroup Analysis

Subgroup analysis will be performed for AEs and changes in DIEPSS total score (excluding overall severity) from baseline at Week 6 (LOCF). The subgroup analysis will include sex and age.

15.3.7 Pharmacokinetic Analysis

15.3.7.1 Double-blind treatment phase

Plasma concentrations of blonanserin and M-1 will be summarized at each visit by treatment group. Plasma concentration ratio of M-1 to blonanserin will be summarized at each visit by treatment group.

15.3.7.2 Open-label treatment phase

Plasma concentrations of blonanserin and M-1 will be summarized at each visit by the last application before the visit. Plasma concentration ratio of M-1 to bonanserin will be summarized at each visit by the last application before the visit.

15.3.7.3 Subgroup Analysis

Subgroup analysis will be performed for plasma concentrations of blonanserin at Week 6 and Week 34. The subgroup analysis will include sex and age. The ratio of the geometric mean of plasma concentrations of blonanserin at Week 6 in elderly adults to non-elderly adults and the corresponding 90% confidence interval will be presented by treatment group. Also, the ratio of the geometric mean of plasma concentrations of blonanserin at Week 34 in elderly adults to non-elderly adults and the corresponding 90% confidence interval will be presented by the last application before the visit.

15.3.8 Handling of data

15.3.8.1 Day 1

Day 1 is defined as the day of the initial application in the double-blind treatment phase.

15.3.8.2 Analysis visits, baseline, and post-baseline measures

All data will be organized and analyzed according to the scheduled timing as outlined in Table 3 to 5 Schedule of Assessments (p10~13) and according to the visit denoted in the CRFs. Unscheduled visits may be used if scheduled visits are not available, and details will be prespecified in the statistical analysis plan before the interim analysis is performed. The baseline data for statistical analyses will be defined as the last non-missing data on or before Day 1. In analysis for the open-label treatment phase and the DSP-5423P treatment period, the baseline data of the subjects in the Placebo group will be defined as the last non-missing data before the beginning of DSP-5423P application. Post-baseline data for statistical analysis will be defined as the non-missing data on or after Day 1 and through 7 days after the date of final

application of the study drug (excluding baseline). The data collected at the discontinuation visit will be mapped to the next scheduled visit of the actual discontinuation date.

15.3.8.3 Missing Data

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.

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 for an analysis of sensitivity. The final post-baseline data in the double-blind treatment phase will be carried forward and will be defined as the Week 6 (LOCF). The final post-baseline value of the entire study duration will be defined as LOCF endpoint for all subjects.

In the safety analysis, the final post-baseline data in the double-blind treatment phase will be carried forward and will be defined as the Week 6 (LOCF). The final post-baseline value of the entire study duration will be defined as the LOCF endpoint for all subjects.

15.4 Interim Analysis

An 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 performed in accordance with the protocol and a charter for the interim analysis which describes well-defined procedures for the interim analysis. Analysis method for interim analysis is outlined in Section 15.4.1 (p71) and will be detailed in an interim analysis plan.

Separated from the formal interim analysis described above, 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 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. Details of the analyses conducted for the regulatory submission will be provided in the statistical analysis plan.

15.4.1 Outlined Interim Analysis

The analysis population for the interim analysis will be mITT population and determined by a blinded data review before the interim analysis. PANSS data at all scheduled visits, discontinuation visits, and unscheduled visits of double-blind treatment phase of the analysis population for the interim analysis will be collected and cleaned. The primary variable for the interim analysis will be the change in PANSS total score from baseline and its treatment difference between DSP-5423P and placebo will be used for estimating the conditional power. The conditional power under an empirical assumption will be compared with the futility boundary of 8%, where the empirical assumption assumes that the observed trend in treatment difference will continue to the end of study[ref.19]. Any safety data will not be reviewed in unblinded manner at the interim analysis.

15.4.2 Independent Biostatistician and Steering Committee

An independent biostatistician will be appointed in a CRO not delegated any study procedure for the study. The Sponsor steering committee (SC) member(s) will be those who are not involved in conducting the study. The charter for the interim analysis will specify roles and responsibilities of the appointed independent biostatistician and the SC, and include procedures to provide the recommendation from the independent biostatistician to the SC, and specify the detailed futility criteria.

The independent biostatistician will perform the interim analysis and make a recommendation to the SC based on interim analysis results and the futility criteria specified in the charter for interim analysis. If the conditional power is below the boundary, the Sponsor will be recommended to early terminate the study for futility, otherwise, to continue the study as planned. The SC is responsible to make a decision whether to continue or early terminate the study. The decision of SC (not including the recommendation) will be informed to the study team.

Data monitoring committee (DMC) will not be organized for the interim analysis because any safety concern of DSP-5423P to require the use of DMC has not been identified from previous and ongoing studies.

15.4.3 Confidentiality of Interim Data and Analyses

For the interim analysis, the randomization code will be revealed only to the appointed independent biostatistician and programmer(s) performing the interim analysis. The independent biostatistician will make the recommendation only to the SC and will not disclose any information revealing unblinded interim results to anyone until the database lock and unblinding thoroughly for the double-blind treatment phase. The SC will also keep the recommendation confidential until the study unblinding.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL /DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1 Data Collection/Electronic Data Capture (EDC)

The study data of subjects who provide informed consent will be captured in the CRFs through the electronic data capture (EDC) system. The users of this system should receive EDC training from the Sponsor or its delegate. The data will be recorded in the CRFs in English as soon as data are available for entry. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

The Sponsor will provide copies of the original CRFs for the Principal Investigator, and he/she will retain them. If data are inconsistent with source documents, the Investigator will clarify the lack of consistency and record the reason. The record will be provided to the Sponsor. The Principal Investigator will keep copies of the record.
If the data need to be revised, the Investigator will comply with the guidance for CRF provided by the Sponsor.

Of the data recorded in the CRF, the source documents of the following can be CRFs per se:

- The outcome, severity, seriousness of AEs
- Causal relationship to the study treatment
- The reasons for concomitant use
- The reasons for dose changing of study drugs
- The reason for discontinuation

16.2 Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its

representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol and in order to comply with ICH GCP and local regulations. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with the source documents available for each subject.

16.3 Audits

The study may be subject to audit by the Sponsor or designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent by signing the ICF. By signing this protocol (affixing a seal with the name on this protocol will be also acceptable in Japan), the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

16.4 Study Documentation

Study records are comprised of source documents, CRFs, and all other administrative documents. A source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications.

16.5 Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis of most of the clinical laboratory tests for this study. The central laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s), and a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens. If an exception is granted to use a local laboratory, the Investigator must supply the Sponsor/CRO with laboratory certification and a current, dated copy of normal range values.

17. ETHICAL AND REGULATORY OBLIGATIONS

<The procedure for Section 17 in Japan is described in the Japan Appendix.>

17.1 Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH Good Clinical Practice (GCP) and the ethical principles that have their origin in the

Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to the Sponsor/CRO the “Investigator Approval" page.

17.2 Institutional Review Board

Documented approval for conducting the study from the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be obtained for all participating centers before initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s). When necessary, an extension, amendment or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor.

A copy of written IRB/IEC approval or a favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to the Sponsor/CRO before start of the study.
The Investigator/CRO is responsible for obtaining from the IRB/IEC continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year or as otherwise specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform the IRB/IEC of all SAEs reported by subjects enrolled in the study or other safety information reported from the Sponsor/CRO in accordance with applicable law(s) and regulation(s).

17.3 Informed Consent

The Investigator will prepare the informed consent form and provide the form to Sponsor/CRO for approval before submission to the IRB. The informed consent form will be approved by the Sponsor/CRO before submission to the IRB.

The Sponsor/CRO may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms

must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be approved by the Sponsor/CRO as well as the IRB.

For patients who are under the adult age based on the local regulation in each country at informed consent, consent should be obtained from the patient's legally acceptable representative (guardian) in addition to the consent from the patient.

Before recruitment and enrollment, each prospective subject and guardian (as needed) will be given a full explanation of the study, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject and guardian (as needed) understand the implications of participating in the study, the prospective subject and guardian (as needed) will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject and guardian (as needed) must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB review, and regulatory inspection. It should be clearly explained to each prospective subject and guardian (as needed) that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study medication, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent form to each subject and guardian (as needed), and will record the date of the informed consent in the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's or guardian's (as needed) consent, the informed consent form must be revised, submitted to the IRB for review and approval or a favorable opinion. The revised informed consent form must be used to obtain consent from a subject and guardian (as needed) currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of approval or a favorable opinion of the protocol amendment.

17.4 Subject Privacy

The Sponsor (or Sponsor's representative) or any designees affirm uphold the subjects confidentiality. The subject will be identified by a unique code only; full names will

be masked before transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations. When any formal presentation or publications of data collected as a direct or indirect result of the study are made, the subject privacy will be protected

17.5 Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or a favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC immediately or in accordance with applicable regulatory requirements.

17.6 Records Retention

The Investigator/the site must arrange for retention of study records at the study center in accordance with applicable regulations and Sponsor SOPs. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the site when the destruction of documents is permitted.

17.7 Inspection of Records

In the event of an inspection, the Investigator agrees to allow the Sponsor, its representative and the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sumitomo Dainippon Pharma Co., Ltd.-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

17.8 Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the coordinating investigators or the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it

is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

17.9 Compensation

If subjects have any adverse event or injury directly resulting from the study medications or procedures, the Sponsor will appropriately compensate in accordance with applicable regulatory requirements.

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