DSP-5423P

Study protocol

Blonanserin
D4904040
Long-Term Study of DSP-5423P in Patients with Schizophrenia
[Phase 3]

Version number :1.02

30 October 2015

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Table 1 emergency contact information1

Role in study	Name	Contact information
Responsible monitor	[redacted]	Sumitomo Dainippon Pharma Co., Ltd. Clinical Development Division, CNS Group, [redacted]

1. SYNOPSIS

Name of Sponsor:	Sumitomo Dainippon Pharma Co., Ltd.
Name of Investigational product:	DSP-5423P
Name of Active ingredient:	Blonanserin
Title of Study (study number):	Long-Term Study of DSP-5423P in Patients with Schizophrenia [Phase III Study] (D4904040)
Planned indication:	Schizophrenia
Phase of development:	Phase III
Study period (planned):	December 2014 ~ July 2017 (Last Date of Registration: May 2016)

Study Objective:

Primary objective:

To evaluate the safety of DSP-5423P (40-80 mg/day) for 52-week treatment.

Secondary objective:

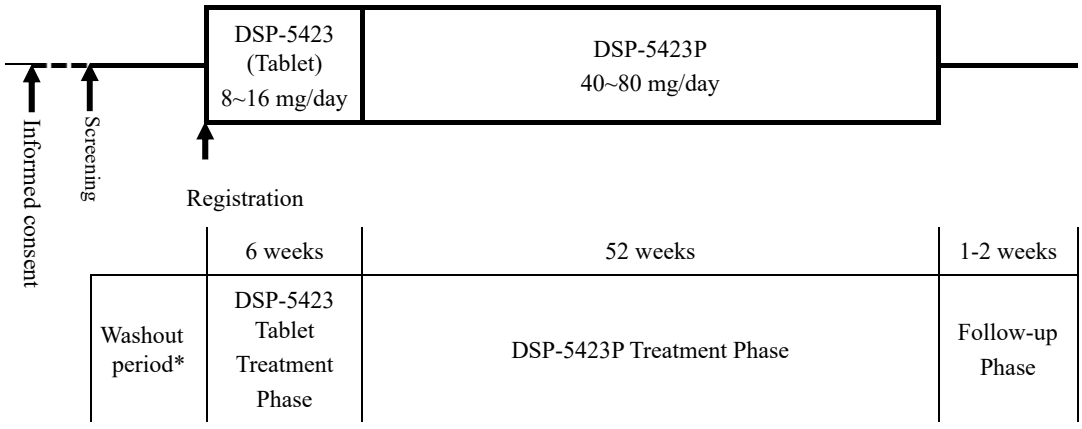
- To evaluate the safety and effectiveness of switching from DSP-5423 (tablet) to DSP-5423P.
- To evaluate the effectiveness and pharmacokinetics of DSP-5423P (40-80 mg/day) for 52-week treatment.

Study design of clinical study:

Multicenter, uncontrolled, open-label, flexible dose

The study contains two cohorts: cohort 1 consists of DSP-5423 (tablet) treatment phase and DSP-5423P treatment phase, and cohort 2 consists of DSP-5423P treatment phase.

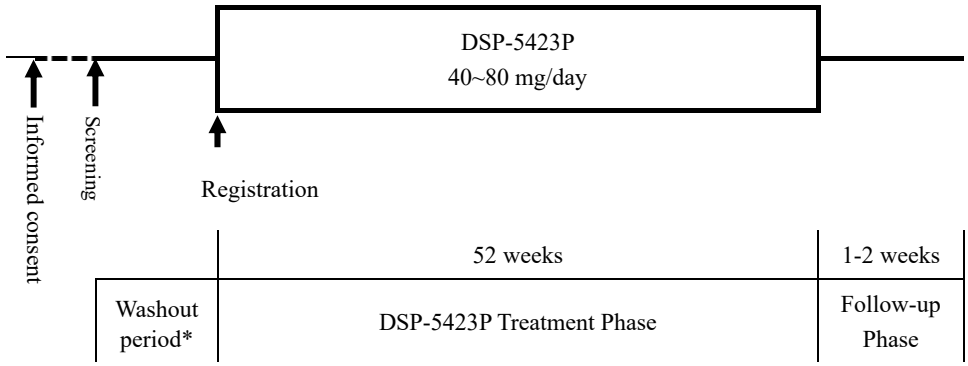
Study schematic (cohort 1)



* Prior to initiation/beginning of DSP-5423 (tablet) administration, washout period (up to 4 weeks) will be arranged

according to the dose of the prior antipsychotics (haloperidol equivalent).

Study schematic (cohort 2)



* Prior to initiation/beginning of DSP-5423P application, washout period (up to 4 weeks) will be arranged according to the dose of the prior antipsychotics (haloperidol equivalent).

Number of Subjects:

Number of subjects of registration: 200

- Number of subjects treated with DSP-5423P for 6 weeks of more in cohort 1: 50 subjects
- Number of subjects treated with DSP-5423P for 52 weeks in cohort 1 and 2: 100 subjects

Diagnosis:

Schizophrenia

Inclusion criteria:

Patients who meet all of the following criteria.

1) Patients who have schizophrenia diagnosed by Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), diagnostic criteria
2) Patients who are aged 18 years or older at informed consent
3) Patients who are fully informed of and understand the objective, 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, and if the patient is hospitalized involuntarily, 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.
4) Patients with premenopausal female and of childbearing potential who have negative result for pregnancy laboratory test (urine) at screening
5) Patients who have informed consent in adequate contraception to prevent pregnancy of the

patients or their partners when they are female of childbearing potential.

Exclusion criteria:

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 topical use), or human immunodeficiency virus (HIV) protease inhibitors.
4) Patients with medical history of hypersensitivity to bronanserin
5) Patients with a history of or current neuroleptic malignant syndromes, tardive dyskinesia or water intoxication
6) Patient with Parkinson's disease
7) Patients with active suicidal ideation or those with a suicide attempt history who are considered ineligible for the study by the Investigator
8) Patients with an HbA1c level (NGSP level) of 8.4% or higher
9) Patients with physical exhaustion accompanied by conditions such as dehydration or malnutrition
10) 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
11) Patients with skin injuries, skin disease, or tattoos at the site of application (back, chest, or abdomen) that precludes adequate patch placement.
12) Patients with a history of drug abuse, drug dependency, alcohol abuse, or alcohol dependency within 6 months (180 days) before screening
13) Patients who received any depot preparation (sustained-release formulation) of antipsychotics within 3 months (90 days) before screening
14) Patients who received clozapine administration within 4 months (120 days) before screening
15) Patients who received administration of blonanserin within 1 Year (365 days) prior to screening and were considered resistant to treatment for blonanserin
16) Patients who received monoamine oxidase (MAO) inhibitor administration within 1 month (30 days) before screening
17) Patients who received electroconvulsive therapy within 6 months (180 days) before screening
18) Pregnant or nursing mother
19) Patients with a history or complication(s) of hypersensitivity to two or more drugs (patients with a history or complication(s) of drug-induced allergic reactions such as anaphylaxis, rash, and urticaria)

20) Patients with medical history or complication(s) of malignant tumor within 5 Years before screening
21) HIV-infected patients
22) Patients who received other investigational product or post-marketing clinical study drugs within 3 months (90 days) before screening, or patients who have enrolled in but not completed other clinical study or post-marketing study before screening
23) Patients who are otherwise considered ineligible for the study by the investigator

Study drug, dose, mode of administration and duration of administration:

Cohort 1:

1) DSP-5423 (tablet) treatment phase

DSP-5423 (tablets) will be administered orally twice daily (after breakfast and evening meal) for 6 weeks. The initial dose of DSP-5423 (tablet) will be 8mg/day. DSP-5423 (tablet) will be administered as flexible dose (8, 12, 16 mg/day) according to the dose adjustment criteria (section 10.2).

2) DSP-5423P treatment phase

DSP-5423P will be applied once daily for 52 weeks. The study drug will be applied to the subject's back, chest, or abdomen. Start DSP-5423P application with the dosage according to the final dosage of DSP-5423 (Table 8 starting dose of DSP-5423P corresponding to DSP-5423 (tablet) final dose). DSP-5423P will be applied as flexible dose (40, 60, 80 mg/day) according to the dose adjustment criteria (section 10.2).

Cohort 2:

DSP-5423P will be applied once daily for 52 weeks. The study drug will be applied to the subject's back, chest, or abdomen. The initial dose of DSP-5423P will be 40 mg/day. DSP-5423P will be applied as flexible dose (40, 60, 80 mg/day) according to the dose adjustment criteria (section 10.2).

Concomitant medications and therapies:

See section 10.3 concomitant medications and therapies for further information.

Restrictions on concomitant medications/therapies from screening until the end of the follow-up phase	From Screening before the study treatment phase	Treatment phase for DSP-5423 (tablet) and DSP-5423P	Follow up phase
MAO inhibitors	A	A	C
CYP3A4 inhibitors (excluding medications for topical use)	A	A	A
CYP3A4 inducers (excluding medications for topical use)	A	A	C
Adrenaline	A	A	A
Other investigational products and Post-Marketed study products	A	A	A
Electroconvulsive therapy	A	A	C
Antipsychotics	B	B	C
Antiparkinson drugs	B	B	C
Antimanic and Antiepileptic Drugs	C	B	C
Hypnotic drugs	C	B	C
Psychotropic drugs (eg. anxiolytic drugs, antidepressants)	C	B	C
Treatment drugs for complication	C	B	C

A: prohibited; B: restricted; C: unrestricted

Abbreviations: MAO=monoamine oxidase, CYP3A4=cytochrome P-450 enzyme 3A4

Before the treatment phase: Before treatment with DSP-5423 (tablet) for cohort 1, or before treatment with DSP-5423P for cohort 2

Study Endpoints:

Efficacy endpoint

1) Change in Positive and Negative Syndrome Scale (PANSS) total score from baseline [note 1)]
2) Change in PANSS subscale total scores from baseline [note 1)]
3) Change in by PANSS 5 Factor Model total score from baseline [note 1)]
4) Change in Clinical Global Impressions–Severity of Illness(CGI-S) scores from baseline [note 1)]
5) Time to treatment discontinuation from the initial application of DSP-5423P

Note 1) Baseline of DSP-5423P treatment phase

Safety endpoint

6) Adverse events (AEs) and adverse drug reaction (ADRs)
7) Extrapyramidal AEs and ADRs
8) Skin-related AEs and ADRs at the application site
9) Assessment of skin irritation reaction at the application site
10) Change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) Total Score (excluding overall severity) from baseline
11) Change in individual DIEPSS scores from baseline
12) Serum prolactin concentration
13) Electrocardiogram (ECG) parameters (QTc)
14) Concomitant use of antiparkinson drug
15) Assessment of suicides using Columbia-Suicide Severity Rating Scale(C-SSRS)
16) Laboratory test values, vital signs and body weight

Pharmacokinetic endpoints

1) Plasma concentration of bronanserin
2) Plasma concentration of bronanserin's metabolites

Other endpoints

1) Total score of Drug Attitude Inventory-10(DAI-10)
2) EuroQol-5 Dimension (EQ-5D) index values.
3) Questionnaire on dosage form

Statistical statistical method:

For efficacy endpoints excluding time to treatment discontinuation from the initial application of DSP-5423P, summary statistics by visit will be provided. Time to treatment discontinuation from the initial application of DSP-5423P will be analyzed using Kaplan-Meier method.

Table 2 Schedule of Assessments (Cohort 1)

			DSP-5423 (tablet) treatment phase (6 weeks)					DSP-5423P treatment phase (52 weeks)													Discontinuation	Follow-up phase (1-2 weeks)
Visit No.	-	1	2	3	4	5	6	101	102	103	104	105	106	107	108	109	110	111	112	113		Follow-up visit
Study timeline [a]	-	Screening	Timeline from initiation of DSP-5423 (tablet) administration					Timeline from initiation of DSP-5423P application													Discontinuation	6 ~ 17 days after completion of treatment or dicontinuation
Week			Tab-Baseline	Tab-Week 1	Tab-Week 2	Tab-Week 4	Tab-Week 6 /baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 36	Week 44	Week 52		
Visit window (Day)		Tab -28-	Tab -2-1	Tab 5-11	Tab 12-18	Tab 26-32	Tab 40-43	5-11	12-18	26-32	40-46	54-60	78-92	106-120	134-148	162-176	190-204	239-267	295-323	351-379	At discontinuation +5	
Obtain informed consent	X																					
Patient demographics and medical history		X																				
Dispense study drug			X[d]	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X			
Study treatment compliance				X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PANSS		X	X[d]	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X[g]	
CGI-S		X	X[d]	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X[g]	
DIEPSS			X[d]	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X[g]	
C-SSRS			X[d]	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X[g]	
DAI-10							X[e]				X						X			X	X	
EQ-5D							X[e]				X						X			X	X	
Skin irritation assessment							X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory test [b]		X	X[d]		X		X[e]		X		X		X		X		X	X	X	X[g]	X[g]	
Pregnancy test [c]		X																		X	X	
12-lead ECG		X	X[d]		X		X[e]		X		X		X		X		X	X	X	X[g]	X[g]	
Body weight		X	X[d]	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body temperature, blood pressure, pulse rate		X	X[d]	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring			←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
Blood sampling for PK					X		X[e]				X						X			X	X	
Questionnaire																				X	X	

a) Tab-Day 1 is defined as the day of the initial administration of DSP-5423 (tablet), and Day 1 is defined as the day of the initial application of DSP-5423P.
b) At Visit 2 (before administration initiation of DSP-5423 (tablet)), Visit 6 (the end of DSP-5423 (tablet) treatment phase) and Visit 113 (the end of DSP-5423P treatment phase), 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.
c) To be performed only in female subjects who are premenopausal and of childbearing potential.
d) Must be performed before the beginning of treatment with DSP-5423 (tablet). For the subject treated with any antipsychotic, must be performed after discontinuation of antipsychotics and before the beginning of treatment with DSP-5423 (tablet).
e) Must be performed before the beginning of treatment with DSP-5423P.
f) If the subject discontinues the study drug during the DSP-5423 (tablet) treatment phase, the subject will undergo the following safety assessments: study treatment compliance, DIEPSS, C-SSRS, laboratory test, pregnancy test, 12-lead ECG, body weight, body temperature, blood pressure, pulse rate, and adverse event monitoring at the discontinuation visit.
g) Must be performed before the initiation of post-treatment with antipsychotics excluding the study drug.

Table 3 Schedule of Assessments (Cohort 2)

			DSP-5423Ptreatment phase (52 weeks)														Discontinuation	Follow-up phase (1-2 weeks)
Visit No.	-	1	2	101	102	103	104	105	106	107	108	109	110	111	112	113		Follow-up visit
Timeline from initiation of DSP-5423P application	-	Screening	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 36	Week 44	Week 52		6 ~ 17 days after completion of treatment or dicontinuation
Visit window (Day)		-28~	-2~1	5~11	12~18	26~32	40~46	54~60	78~92	106~120	134~148	162~176	190~204	239~267	295~323	351~379	At discontinuation +5	
Obtaining informed consent	X																	
Patient demographics and medical history		X																
Dispense study drug			X[d]	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[d]	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X[e]	
CGI-S		X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X[e]	
DIEPSS			X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X[e]	
C-SSRS			X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X[e]	
DAI-10			X[d]				X						X			X	X	
EQ-5D			X[d]				X						X			X	X	
Skin irritation assessment			X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory test [b]		X	X[d]		X		X		X		X		X	X	X	X[e]	X[e]	
Pregnancy laboratory test [c]		X														X	X	
12-lead ECG		X	X[d]		X		X		X		X		X	X	X	X[e]	X[e]	
Body weight		X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body temperature, blood pressure, pulse rate		X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring			←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Blood sampling for PK							X						X			X	X	
Questionnaire																X	X	

a) The Day 1 is defined as the day of the initial application of DSP-5423P.

b) At Visit 2 (before the initiation of DSP-5423P) and Visit 113 (the end of DSP-5423P treatment phase), 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.

c) To be performed only in female subjects who are premenopausal and of childbearing potential.
d) Must be performed before the beginning of treatment with DSP-5423P. For the subject treated with any antipsychotic, must be performed after discontinuation of antipsychotics and before the beginning of treatment with DSP-5423P.
e) Must be performed before the beginning of post-treatment with antipsychotics excluding the study drug.

2. Table of contents, list of tables, and list of figures

Tables of contents

List of tables

List of figures

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 4.

Table 4 List of abbreviations

Abbreviation	Full form
ALT	Alanine aminotransferase
ALP	Alkaline phosphatas (alkaline phosphatase)
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CGI-S	Clinical Global Impression –Severity of Illness
CK	Creatine phosphokinase
Cl	Clorine
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P-450 enzyme
DAI-10	Drug Attitude Inventory-10
DIEPSS	Drug-Induced Extrapyramidal Symptoms Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiogram
EDC	Electronic data capture
EQ-5D	EuroQol-5 Dimension
GCP	Good Clinical Practice
γ-GTP	γ-glutamyl transpeptidase
HbA1c	Hemoglobin A1c
HIV	Human immunodeficiency virus
IPDs	Important protocol deviations
IRB	Institutional Review Board(institutional review board)
K	Potassium
LDH	Lactate dehydrogenase
MAO	Monoamine oxidase
Na	Sodium
NGSP	National Glycohemoglobin Standardization Program
PANSS	Positive and Negative Syndrome Scale
PET	Positron emission tomography

Abbreviation	Full form
PK-PD	Pharmacokinetics-Pharmacodynamics
QTc	QT interval corrected for heart rate
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 α1, 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 D2 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.

Considering these results, a phase 3 confirmatory study is currently being conducted in a randomized double-blind, placebo-controlled, parallel-group manner to confirm the superiority to placebo in order to evaluate the efficacy and safety of DSP-5423P.

The phase 3 long-term study is designed to evaluate (1) the long-term safety, effectiveness and pharmacokinetics of DSP-5423P, (2) the safety and effectiveness of switching from DSP-5423 (tablet) to DSP-5423P in patients with schizophrenia. The clinical study is an uncontrolled, open-label study consisting of cohort 1 with DSP-5423P applied for 52 weeks after administration of the DSP-5423 (tablet) for 6 weeks and cohort 2 with DSP-5423P applied for 52 weeks. The dose of DSP-5423P should be 40-80 mg/day, and the dose of DSP-5423 (tablet) should be 8-16 mg/day, the approved dose for maintenance.

5. Objective of the study

5.1 Primary objective

To evaluate the safety of DSP-5423P (40-80 mg/day) for 52-week treatment.

5.2 Secondary objective

- To evaluate the safety and effectiveness of switching from DSP-5423 (tablet) to DSP-5423P.
- To evaluate the effectiveness and pharmacokinetics of DSP-5423P (40-80 mg/day) for 52-week treatment.

6. Endpoints

6.1 Efficacy endpoints

1) Change in PANSS total score from baseline [note 1)]
2) Change in PANSS subscale total scores from baseline [note 1)]
3) Change in by PANSS 5 Factor Model [note 2)] total score from baseline [note 1)]
4) Change in CGI-S scores from baseline [note 1)]
5) Time to treatment discontinuation from the initial application of DSP-5423P

Note 1) Baseline of DSP-5423P treatment phase
Note 2) PANSS 5 factors model [ref 9)]

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

6.2 Safety endpoints

1) Adverse events (AEs) and adverse drug reaction (ADRs)
2) Extrapyramidal AEs and ADRs
3) Skin-related AEs and ADRs at the application site
4) Assessment of skin irritation reaction at the application site
5) Change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) Total Score (excluding overall severity) from baseline
6) Change in individual DIEPSS scores from baseline
7) Serum prolactin concentration
8) Electrocardiogram (ECG) parameters (QTc)
9) Concomitant use of antiparkinson drug

10) Assessment of suicides using Columbia-Suicide Severity Rating Scale(C-SSRS)
11) Laboratory test values, vital signs and body weight

6.3 Pharmacokinetic endpoints

- Plasma concentration of bronanserin
- Plasma concentration of bronanserin's metabolites note1)

Note 1) metabolite to be measured
Cohort 1: M-1 (N-de-ethylated metabolite), M-2 (N-oxidezed metabolite), M-3 (7OH) (hydroxided metabolite), M-3 (8OH) (hydroxided metabolite), M-4 (ethylenediaminated metabolite), and M-8 (carboxylic acid).
Cohort 2: M-1 (N-de-ethylated metabolite)

6.4 Other endpoints

1) Drug Attitude Inventory-10 (DAI-10) summed scores.
2) EuroQol-5 Dimension (EQ-5 D) utility values.
3) Questionnaire on dosage form

7. Investigational Plans

7.1 Overall study design of clinical study

This clinical study is a multicenter, uncontrolled, open-label, long-term administration study consisting of two cohorts. The study schematics of clinical study are presented in Figures 1 (cohort 1) and 2 (cohort 2). Details of the study assessment and other procedures (assessment, observation, laboratory test) to be performed are presented in Tables 2 (cohort 1), 3 (cohort 2) and Chapter 11. In both cohorts, Day 1 is defined as the day of the initial application of DSP-5423P.

Cohort 1, consisting of DSP-5423 (tablet) treatment phase and DSP-5423P treatment phase, and cohort 2, consisting only of DSP-5423P treatment phase, will be conducted in different subjects, and cohort 2 will be initiated after enrollment in cohort 1 has been completed. Enrollment in cohort 1 will be terminated when the number of total subjects whose DSP-5423P treatment duration is 6 weeks or more reached 50. At the completion of enrollment in cohort 1 and at the initiation of enrollment in cohort 2, the sponsor will notify the participating study centers of that.

7.1.1 Cohort 1

Cohort 1 consists of 3 phases: DSP-5423 (tablet) treatment phase (6 weeks), DSP-5423P treatment phase (52 weeks) and follow-up phase (1-2 weeks). Prior to initiation of DSP-5423 (tablet) treatment phase, washout period (up to 4 weeks) will be arranged (see Section 10.3.3.1) according to the dose of prior antipsychotics (haloperidol equivalent).

DSP-5423 (tablet) treatment phase

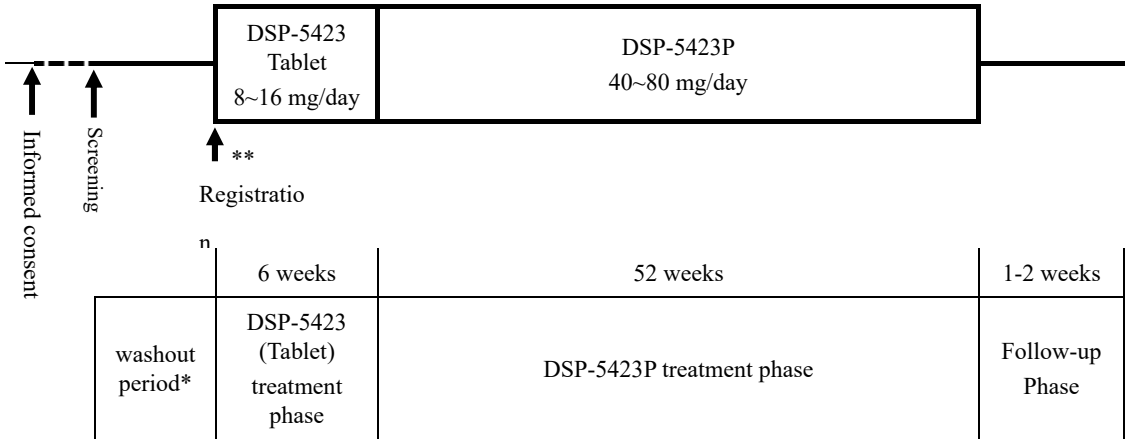
DSP-5423 (tablets) will be administered orally twice daily after breakfast and evening meal

for 6 weeks. The initial dose of DSP-5423 (tablet) will be 8mg/day. DSP-5423 (tablet) will be administered as flexible dose (8, 12, 16 mg/day) according to the dose adjustment criteria (section 10.2).

DSP-5423P treatment phase

DSP-5423P will be applied once daily for 52 weeks. The study drug will be applied to the subject's back, chest, or abdomen. Start DSP-5423P application with the dosage according to the final dosage of DSP-5423 (Table 8 starting dose of DSP-5423P corresponding to DSP-5423 (tablet) final dose). DSP-5423P will be applied as flexible dose (40, 60, 80 mg/day) according to the dose adjustment criteria (section 10.2).

Figure 1 Study schematic (cohort 1)



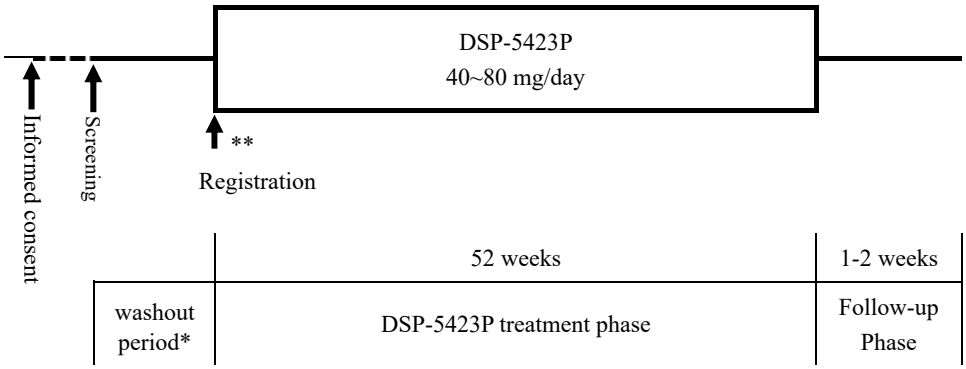
* If the dose of the prior antipsychotics is 12.0 mg/day or less (haloperidol equivalent), to initiate the administration of the DSP-5423 (tablet) after termination of the prior antipsychotics. Washout period may be arranged and down-titration would be done as needed prior to termination.
If the dose of the prior antipsychotics exceeds 12.0 mg/day (haloperidol equivalent), washout period will be arranged. First, the dose is reduced to 12.0 mg/day or less, then down-titration would be done as needed. After termination of the prior antipsychotics, to initiate the administration of the DSP-5423 (tablet).
Washout period should be up to 4 weeks (28 days) from the screening.

** The registration procedure is presented in section 10.

7.1.2 Cohort 2

Cohort 2 consists of 2 phase: DSP-5423P treatment phase (52 weeks) and follow-up phase (1-2 weeks). During the DSP-5423P treatment phase, DSP-5423P will be applied once daily for 52 weeks. The study drug will be applied to the subject's back, chest, or abdomen. The initial dose of DSP-5423P will be 40 mg/day. DSP-5423P will be applied as flexible dose (40, 60, 80 mg/day) according to the dose adjustment criteria (section 10.2). Prior to initiation of DSP-5423P treatment phase, a washout period (up to 4 weeks) will be arranged (see Section 10.3.3.1) according to the dose of prior antipsychotics (haloperidol equivalent).

Figure 2 Study schematic (cohort 2).



* If the dose of the prior antipsychotics is 12.0 mg/day or less (haloperidol equivalent), to initiate the application of the DSP-5423P after termination of the prior antipsychotics. Washout period may be arranged and down-titration would be done as needed prior to termination.

If the dose of the prior antipsychotics exceeds 12.0 mg/day (haloperidol equivalent), washout period will be arranged. First, the dose is reduced to 12.0 mg/day or less, then down-titration would be done as needed. After termination of the prior antipsychotics, to initiate the administration of the DSP-5423P.

Washout period should be up to 4 weeks (28 days) from the screening.

** The registration procedure is presented in section 10

7.2 Rationale

7.2.1 Rationale for the study design

The study is designed to evaluate the long-term safety and effectiveness of DSP-5423P as an uncontrolled open-label study with treatment duration of 52 weeks. The dosage of DSP-5423 (tablet) and DSP-5423P was selected as flexible-dose.

Switching from oral bronanserin to DSP-5423P is potential regimen when DSP-5423P is marketed. In addition, in the result of a phase II study (PET study, D4904019) which was conducted in order to evaluate dopamine D_2 receptor occupancy by positron emission tomography (PET) in patients with schizophrenia, the result suggests that a higher concentration of plasma bronanserin than DSP-5423 (tablet) is needed for DSP-5423P to achieve a similar dopamine D_2 receptor occupancy as DSP-5423 (tablet). Therefore, we decided to design a DSP-5423P treatment phase after DSP-5423 (tablet) treatment phase that the initial dose of DSP-5423P is determined by the final dose of DSP-5423 (tablet)

in order to evaluate the effect of safety and effectiveness in the case of the switching from oral bronanserin to DSP-5423P

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7.2.2 Rationale of dose, mode of administration and duration of administration

DSP-5423P

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 -80 mg/day are to be used in this study.

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).

Based on the Yakushin (Pharmaceutical Affairs Bureau Examination Division : PAB/ED) notification No. 592 of May 24th 1995, "Recommendation on the numbers of patients and duration of exposure for the safety evaluation of drugs intended for the long-term treatment of non-lifethreatening conditions" one year (52 weeks) was selected as the duration of administration.

DSP-5423 (tablets)

Based on the approved dose of blonanserin tablet, the initial dose of DSP-5423 (tablet) was set at 8 mg/day and the dose was increased or decreased according to the maintenance dose (8-16 mg/day). Oral administration was planned after meal (in the morning and in the evening) in accordance with the approved treatment regimen of blonanserin tablet.

Since initial dose was set at 8 mg/day, it was considered necessary to determine the optimal dose

for 2 weeks. It has been reported that the treatment response assessment of antipsychotics should be performed 2 to 4 weeks after administration initiation [ref 11)]. Furthermore, in the clinical studies of DSP-5423 (tablets) conducted in Japan, most of the common/frequent adverse events, including akathisia, tremors, insomnia, and increased blood prolactin, have been observed in 4 weeks after administration initiation. Therefore, 6-week was set as the duration enough to collect effectiveness and safety data on DSP-5423 (tablet).

7.2.3 Rationale of endpoints

Efficacy endpoints

PANSS and CGI-S, which are frequently used as endpoints in the clinical study of antipsychotics, were set. In addition, because treatment of antipsychotics is often terminated due to adverse drug reaction and/or lack of efficacy, we considered that duration of DSP-5423P would be helpful in evaluating the effectiveness of antipsychotic drugs and decided to be endpoints.

Pharmacokinetic endpoints

To investigate the pharmacokinetics of DSP-5423P application, bronanserin and the main metabolite, M-1, are measured in both cohort 1 and cohort 2. In addition, in cohort 1, the metabolites other than M-1 are also measured in order to compare the pharmacokinetics of DSP-5423P application with that of DSP-5423 (tablet) administration, which has a higher metabolite production ratio, in the same subject.

Safety endpoints

Since DSP-5423P is transdermal formulation, skin-related adverse event/ adverse drug reaction at the application site and skin irritation assessment were set.

Other endpoints

Because DAI-10 is one of the commonly used measures of adherence, and because EQ-5D is one of the commonly used measures of health-related Quality of life (QOL) as a comprehensive measure, DAI-10 and EQ-5D were set. In addition, questionnaires on the dosage form were set to investigate the impressions of subject on the DSP-5423P.

7.3 Measures to prevent missing data

The following study design and conduct elements are implemented in an effort to minimize the number of subjects who are terminated from the study before the completion;

1) Depending on the dose of prior antipsychotics, washout period can be arranged.
2) Adequately wide visit windows were set for each Visit.
3) During the entire study period, concomitant use of antiparkinson drugs, lorazepam, and hypnotic drugs are allowed for extrapyramidal symptoms, psychiatric symptoms, and insomnia respectively.
4) Rescue use of antipsychotics is allowed for urgent psychiatric symptoms.

5) Flexible dose adjustment is allowed based on effectiveness or tolerability.
6) 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.
7) Monitor data collection for adherence during the study.

7.4 Scheduled duration of clinical study

December 2014 ~July 2017 (Enrollment period: ~ May 2016)

8. Subject selection

8.1 Inclusion criteria

Patients who meet all of the following criteria.

1) Patients who have schizophrenia diagnosed by Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), diagnostic criteria
2) Patients who are aged 18 years or older at informed consent
3) Patients who are fully informed of and understand the objective, 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, and if the patient is hospitalized involuntarily, 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.
4) Patients with premenopausal female and of childbearing potential who have negative result for pregnancy laboratory test (urine) at screening
5) Patients who have informed consent in adequate contraception to prevent pregnancy of the patients or their partners when they are female of childbearing potential.

8.2 Exclusion criteria

Exclusion from this clinical study if any of the following applies:

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 topical use), or human immunodeficiency virus (HIV) protease inhibitors.
4) Patients with medical history of hypersensitivity to bronanserin

5) Patients with a history of or current neuroleptic malignant syndromes, tardive dyskinesia or water intoxication
6) Patient with Parkinson's disease
7) Patients with active suicidal ideation or those with a suicide attempt history who are considered ineligible for the study by the Investigator
8) Patients with an HbA1c level (NGSP level) of 8.4% or higher
9) Patients with physical exhaustion accompanied by conditions such as dehydration or malnutrition
10) 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
11) Patients with skin injuries, skin disease, or tattoos at the site of application (back, chest, or abdomen) that precludes adequate patch placement.
12) Patients with a history of drug abuse, drug dependency, alcohol abuse, or alcohol dependency within 6 months (180 days) before screening
13) Patients who received any depot preparation (sustained-release formulation) of antipsychotics within 3 months (90 days) before screening
14) Patients who received clozapine administration within 4 months (120 days) before screening
15) Patients who received administration of blonanserin within 1 Year (365 days) prior to screening and were considered resistant to treatment for blonanserin
16) Patients who received monoamine oxidase (MAO) inhibitor administration within 1 month (30 days) before screening
17) Patients who received electroconvulsive therapy within 6 months (180 days) before screening
18) Pregnant or nursing mother
19) Patients with a history or complication(s) of hypersensitivity to two or more drugs (patients with a history or complication(s) of drug-induced allergic reactions such as anaphylaxis, rash, and urticaria)
20) Patients with medical history or complication(s) of malignant tumor within 5 Years before screening
21) HIV-infected patients
22) Patients who received other investigational product or post-marketing clinical study drugs within 3 months (90 days) before screening, or patients who have enrolled in but not completed other clinical study or post-marketing study before screening
23) Patients 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 used in the study are shown in Tables 5 and Table 6. The study drugs will be transdermal patches (DSP-5423P 20 mg patches, DSP-5423P 40 mg patches) covered with a transparent protective liner on their adhesive side. DSP-5423 Tablets 2 mg and DSP-5423 Tablets 4 mg are white tablets.

Table 5 DSP-5423P

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

TABLE 6 DSP-5423 (TABLETS)

Study drug	Unit dose of Blonanserin
DSP-5423 Tablets 2 mg	2 mg
DSP-5423 Tablets 4 mg	4 mg

9.2 Study drug packaging and labeling

9.2.1 Packaging description

DSP-5423P and DSP-5423 (tablets) will be packaged in paper boxes.

(1) DSP-5423P

A paper box, for DSP-5423P20 mg and DSP-5423P 40 mg each, contains 60 aluminum-laminated study drug patches (1 patch in each laminate).

(2) DSP-5423 (tablets)

1) PTP sheet

DSP-5423 Tablets 2 mg: Packaging 21 study drug tablets in one sheet.

DSP-5423 Tablets 4 mg: Packaging 14 study drug tablets in one sheet.

2) Paper box

A paper box, for DSP-5423 Tablets 2 mg and DSP-5423 Tablets 4 mg each, contains 10 sheets.

9.2.2 Labeling description

Paper boxes for the study medications will be labeled as clinical trial use only, compound/code or name of investigational drug (DSP-5423P or DSP-5423), Lot No., Storage conditions, expiration date,

sponsor's name and address.

9.3 Study drug storage

All study drugs should be stored under appropriate storage conditions in a secure location to which only the Investigators and designated persons have access. The appropriate storage conditions for study drugs storage will be specified in the guidance for drug accountability provided by the sponsor.

9.4 Dispensing of study drug

The Investigators will dispense the study drug to be used until the next visit to the subject at the current study visit.

9.5 Study drug accountability

Sponsor will dispense the study drug to designated persons after the clinical study contract between sponsor and the site has been concluded. The study drug will be stored and managed in accordance with the guidance procedures and the designated persons at the site is responsible for maintaining adequate records of drug disposition in order to control the status of study drug use. Study drug should not be used other than the clinical study.

9.6 Study drug handling and disposal

The designated persons for handling of the study drug at the site should handle the study drug in accordance with the guidance for drug accountability. If there is study drug of unused or return from subject, the designated persons are required to return all unused study drugs to the sponsor as instructed. In the event that a study drug is accidentally disposed of or lost at the site, the designated persons will report study drug disposal or loss to the sponsor while recording in the drug accountability records.

The designated persons will provide a copy of the drug accountability records to the sponsor after completion of study drug administration and application. The sponsor ensures that the drug accountability records, the quantity of study drug that has been unused or returned from a subject, and the content of the case report form are consistent. If there is any inconsistency, the Primary investigator is required to immediately investigate the cause and take the necessary action.

10. Treatment of subjects

Identification and registration of the subject will be carried out according to the following procedures.

(1) Subject identification number assignment

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.

(2) Eligibility confirmation (Screening test) and Enrollment

1) Investigator will conduct screening test, assessments, observations, and laboratory/ECG tests for a subject who provides informed consent at the screening (Visit 1) in Table 2 (cohort 1) or Table 3 (cohort 2) to confirm the subject's eligibility.
2) Investigator will resister eligible subject to the subject registry system. In the case that wash-out period is required, Investigator will register a subject after dose reduction of prior antipsychotics is completed and study drug administration/application is judged to be feasible by the Investigator.

In cohort 1, Investigator will register a subject transition to DSP-5423P application period to the subject registry system after conducting assessments, observations and lab/ECG tests at Visit 6 in DSP-5423 (tablet) administration period (Table 2) but will do this before initiation of DSP-5423P application.

10.1 Study medication

10.1.1 Cohort 1

(1) DSP-5423 (tablet) administration period (6 weeks)

Oral administration of DSP-5423 (tablets) twice a day after meals (morning and evening) for 6 weeks. Starting dose is 8 mg/day and daily dose will be adjusted appropriately at 8 mg/day, 12 mg/day or 16 mg/day based on the dose adjustment criteria (Section 10.2), taking into account the symptom and safety of subject. If prior antipsychotics are administered, start the administration of DSP-5423P after wash-out of prior antipsychotics in accordance with the restricted concomitant drug (Section 10.3.3.1, Antipsychotics).

TABLE 7 DSP-5423 (TABLET) COMBINATIONS

Dose		DSP-5423 (tablet) combinations per dose	
Per day	Per dose		
8 mg/day	4 mg/dose	DSP-5423 Tablets 4 mg: 1 tablet	●
12 mg/day	6 mg/dose	DSP-5423 Tablets 2 mg: 3 tablets	○○○
16 mg/day	8 mg/dose	DSP-5423 Tablets 4 mg: 2 tablets	●●

○: DSP-5423 Tablet 2 mg; ●: DSP-5423 Tablet 4 mg

(2) DSP-5423P application period (52 weeks)

DSP-5423P will be applied once a day for 52 weeks. The application site will be either the subject's back, chest or abdomen, and all DSP-5423P of the one-day supply should be applied daily at the same

time. The guidance for application of DSP-5423P is shown in Section 10.1.3.

Table 8 shows the dose of the DSP-5423P corresponding to the final dose (dose at Visit 6) of DSP-5423 (tablet). After initiation of the DSP-5423P application with a dose corresponding to the final dose of DSP-5423 (tablet), the dose should be increased or decreased at 40 mg/day, 60 mg/day, or 80 mg/day according to the dose adjustment criteria (Section 10.2). DSP-5423P combinations are shown in Table 9.

Table 8 starting dose of DSP-5423P corresponding to DSP-5423 (tablet) final dose

DSP-5423 (tablet) final dose	DSP-5423Pinitiation/beginning dose
8 mg/day	40 mg/day
12 mg/day	60 mg/day
16 mg/day	80 mg/day

DSP-5423 (tablet) final dose: DSP-5423 (tablet) dose at Visit 6

TABLE 9 DSP-5423P combinations

Dose	DSP-5423P combinations		Number of patches per Date
40 mg/day	DSP-5423P 40 mg: 1 sheet	■	1
60 mg/day	DSP-5423P 20 mg: 1 sheet DSP-5423P 40 mg: 1 sheet	□■	2
80 mg/day	DSP-5423P 40 mg: 2 sheets	■■	2

□ :DSP-5423P 20 mg、■:DSP-5423P 40 mg

10.1.2 Cohort 2

DSP-5423P is applied once a daily for 52 weeks. The application site will be either the subject's back, chest or abdomen, and all DSP-5423P of the one-day supply should be applied daily at the same time. The guidance for application of DSP-5423P is shown in Section 10.1.3.

After initiation with 40 mg of DSP-5423P per day, the dose should be increased or decreased to 40 mg/day, 60 mg/day, or 80 mg/day according to the dose adjustment criteria (Section 10.2). DSP-5423P combinations are shown in Table 9.

If prior antipsychotics are administered, start the administration of DSP-5423P after wash-out of prior antipsychotics in accordance with the restricted concomitant drug (Section 10.3.3.1, Antipsychotics).

10.1.3 The guidance for application of DSP-5423P

In both cohort 1 and 2, the subject will be instructed regarding DSP-5423P application as below:

1) The DSP-5423P will be applied directly to normal healthy skin after removing the transparent liner.
2) DSP-5423P will be replaced every day. When DSP-5423P patches are replaced, new DSP-5423P will be applied as soon as possible In addition, 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.
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 DSP-5423P will be protected from water. Before taking a bath or shower, DSP-5423P should be removed. After taking a bath or shower, new patches 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 DSP-5423P application until the follow-up visit.
6) No other adhesive skin patches are to be overlaid on the current application site of DSP-5423P. No liniments should be used at the current application site of DSP-5423P. The study drug should not be applied to any site where liniments are used.
7) Surgical tape should be used to maintain DSP-5423P 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.

10.2 Dose adjustment criteria

The DSP-5423P dose can be increased or reduced by 20 mg/day at each adjustment within a range of 40 mg/day, 60 mg/day or 80 mg/day according to the following dose adjustment criteria. The DSP-5423 (tablet) dose can be increased or reduced by 4 mg/day at each adjustment within a range of 8 mg/day, 12 mg/day or 16 mg/day according to the following dose adjustment criteria.

Regulatory Assessment timing

- When the CGI-S score is between 4 and 7 and when no safety concerns arise, the DSP-5423P/DSP4323 (tablet) 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/DSP4323 (tablet), the DSP-5423P/DSP4323 (tablet) dose can be increased.

As necessary

- When the Investigator considers a higher dose of DSP-5423P/DSP4323 (tablet) to be necessary due to insufficient efficacy, the DSP-5423P/DSP4323 (tablet) dose can be increased.
- When the Investigator considers a lower dose of DSP-5423P/DSP4323 (tablet) to be necessary due to the AEs, the DSP-5423P/DSP4323 (tablet) dose can be reduced.

PANSS and CGI-S should be evaluated before the dose adjustment at each unscheduled visit (Section 11.2 Efficacy Assessments). DIEPSS should be evaluated as well as PANSS and CGI-S when the DSP-5423P/DSP4323 (tablet) dose is reduced due to extrapyramidal symptoms (Section11.3 Safety Assessments).

After the dose adjustment, the Investigator will record the reason for the dose adjustment in the CRFs. The DSP-5423P/DSP4323 (tablet) 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 initiation of DSP-5423 administration until the follow-up visit in cohort1 or initiation of DSP-5423P application until the follow-up visit in cohort 2 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 and during wash-out period will also be recorded in the CRFs

In this section (Section 10.3), beginning of DSP-5423 (tablet) administration in cohort 1 or beginning of the DSP-5423P application in cohort 2 is defined as "beginning of study drug administration/application".

Table 10 shows restrictions on concomitant medications/therapies.

Table 10 Restrictions on concomitant medications/therapies

	From screening before beginning of study drug administration/application	DSP-5423 (tablet) administration period and DSP-5423P application period	Follow-up period
MAO inhibitors	A	A	C
CYP3A4 inhibitors (External drugs for topical use can be used.)	A	A	A
CYP3A4 inducers (External drugs for topical use can be used.)	A	A	C
Adrenaline	A	A	A
Other investigational products or post-marketed study products	A	A	A
Electroconvulsive therapy	A	A	C
Antipsychotics	B	B	C
Antiparkinson drug	B	B	C
Antimanic and Antiepileptic Drugs	C	B	C
Hypnotic drug	C	B	C
Psychotropic drugs (such as antianxiety drugs and antidepressants)	C	B	C
Treatment drugs for complication	C	B	C

A: prohibited; B: restricted; C: unrestricted
Abbreviations: MAO=monoamine oxidase, CYP3A4=cytochrome P-450 enzyme 3A4
Beginning of study drug administration/application: beginning of DSP-5423 (tablet) administration in cohort 1 or beginning of the DSP-5423P application in cohort 2

10.3.1 Prohibited concomitant medications

Taking 1) to 5) below will be prohibited from screening until completion of all assessment at last visit or discontinuation visit (Visit113) in DSP-5423P application period. In addition, taking 3) to 5) below will be prohibited until the follow-up visit.

1) Monoamine oxidase (MAO) inhibitors
2) 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.
3) CYP3A4 inhibitors (eg, itraconazole, fluconazole, erythromycin, foods and beverages containing grapefruit). External drugs for topical use can be used with no restrictions.
4) Adrenaline
5) Other investigational products or post-marketing clinical study products

10.3.2 Prohibited Therapies

Electroconvulsive therapy will be prohibited from screening until completion of assessments at the last visit (Visit 113) or the discontinuation visit in DSP-5423P application period.

10.3.3 Restrictions on concomitant medications

10.3.3.1 Antipsychotics

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

1) For the subjects not treated with antipsychotics at screening

   Antipsychotics will be prohibited from screening until completion of assessments at the last visit (Visit 113) of the DSP-5423P application period or the discontinuation visit.

2) For the subjects treated with any antipsychotics at screening (prior antipsychotics)

   The antipsychotics should be tapered and completely discontinued according to procedures a) or b) below, the study drug administration/application will be started. The wash-out period for tapering prior antipsychotics should be up to 4 weeks (28 days) from the screening. Antipsychotics will be prohibited from beginning of study drug administration/application until completion of assessments at the last visit (Visit 113) of the DSP-5423P application period or the discontinuation visit.

   a) If the prior antipsychotics dose is 12.0 mg/day or less (haloperidol equivalent)

      The prior antipsyochotics should be completely discontinued, through tapering during the wash-out period, if needed.

   b) If the prior antipsychotics dose is over 12.0 mg/day (haloperidol equivalent)

      The prior antipsyochotics should be tapered. After the dose of the prior antipsychotics is 12 mg/day or less (haloperidol equivalent), these antipsychotics should be completely discontinued, through tapering during the wash-out period, if needed.

If urgent treatment is required because of psychiatric symptoms such as acute psychomotor excitability, 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 should be 10 days or less through DSP-5423 (tablet) administration period and DSP-5423P application period.

10.3.3.2 Antiparkinson drugs

Antiparkinson drugs will be restricted as follows:

1) For the subjects not treated with antiparkinson drugs at screening

   Antiparkinson drugs will be prohibited from screening until completion of assessments at the last visit (Visit 113) of the DSP-5423P application period or the discontinuation visit.

2) For the subjects treated with antiparkinson drugs at screening

   Antiparkinson drugs will be tapered and completely discontinued before beginning of the study drug administration/application. Antiparkinson drugs will be prohibited from the

beginning of the study drug administration/application until completion of assessments at the last visit (Visit 113) of the DSP-5423P application period or the discontinuation visit.

If extrapyramidal symptoms occur or worsen during the DSP-5423 (tablet) period or DSP-5423P application period, 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.

Note that for the subjects who started the administration of antiparkinson due to extrapyramidal symptom occurred or worsen during the DSP-5423 (tablet) period in cohort 1, if the subject continued the antiparkinson drugs at transition to the DSP-5423P application period, the antiparkinson drugs should be tapered and discontinued in 2 weeks beginning of the DSP-5423P application, as much as possible.

TABLE 11 Permitted concomitant antiparkinson drugs

Trihexyphenidyl
Biperiden
Promethazine

10.3.3.3 Antimanic and Antiepileptic Drugs

Antimanic and antiepileptic drugs will be restricted as follows:

1) For the subjects not treated with antimanic or antiepileptic drugs at screening

   Administration should be avoided whenever possible from screening until completion of assessments at the last visit (Visit 113) of the DSP-5423P application period or the discontinuation visit

2) For the subjects treated with antimanic or antiepileptic drugs at screening

   The regimen will not be changed as much as possible from beginning of study drug administration/application until completion of assessments at the last visit (Visit 113) of the DSP-5423P application period or the discontinuation visit

If the psychiatric symptoms improve, antimanic and antiepileptic drugs may be tapered or discontinued.

10.3.3.4 Hypnotic drugs

When insomnia occurs or worsens during the DSP-5423 (tablet) period or DSP-5423P application period, the hypnotic drugs will be permitted. While the drugs listed in Table 12 are recommended, other benzodiazepine receptor agonists may be used. However, all hypnotic drugs will be prohibited within 12 hours before the PANSS, CGI-S, and C-SSRS assessments.

If the insomnia improves, hypnotic drugs may be tapered or discontinued.

Table 12 Permitted concomitant hypnotic drugs

Eszopiclone
Zopiclone
Zolpidem
Triazolam
Brotizolam
Rilmazafone
Lormetazepam

10.3.3.5 Psychotropic drugs (eg, anxiolytics, antidepressants)

When psychiatric symptoms, such as anxiety, agitation and irritation, occur during the DSP-5423 (tablet) period or DSP-5423P application period, 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.

10.3.4 Medications for complications

All drugs used for the treatment for complications (eg, hypertension, hyperlipidemia, diabetes) at screening should be continued without any dosage modification as much as possible from beginning of study drug administration/application until the last visit (Visit 113) of DSP-5423P application period or the discontinuation visit. If the complications worsen or improve, the dosage of the concomitant drugs for these complications may be changed accordingly.

10.4 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.

10.5 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 administrations and the number of administered tablets for each dose during the DSP-5423 (tablet) administration period.

The Investigator will record the dates of the initial and final applications and the number of applied

patches for each dose during theDSP-5423P application period, and the date of final removal of the study drug.

10.6 Treatment Assignment and Blinding

This study is not a randomized study. All subject will be unblinded and will receive the same study drug administration/application with dose adjusted for each cohort.

11. STUDY ASSESSMENTS

A study schematic is presented in Figure 1 and Figure 2. A summary of assessments to be conducted at each visit is presented in Table 2 and Table 3 Schedule of Assessments. Assessments will be conducted within the time frames specified. The timeframes will be calculated from the initiation date of DSP-5423P application for each subject in both cohort 1 and 2. In the DSP-5423 (tablet) administration period of cohort 1, however, it will be calculated from the initiation date of DSP-5423 (tablet) administration for each subject.

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, and inpatient/outpatient status 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. When the efficacy assessments are conducted, the concomitant use of restricted medications will be recorded in the CRFs.

11.2.1 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 and will be certified by the Sponsor

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.

11.2.2 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.

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.

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

11.3.2 DIEPSS

The DIEPSS[ref17)] 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.

11.3.3 C-SSRS

The C-SSRS [ref 18] 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 13

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 13 Scoring of Skin Reactions[ref.19]

Skin condition	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.

Table 14 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

Guidance for Blood Sample Collection

Blood samples will be collected under fasting conditions (at least 10 hours after the last meal) at Visit 2 (before beginning of study drug administration/application in the cohort 1 and the cohort 2 each), Visit 6 of the cohort 1 (end of the DSP-5423 (tablet) administration) and Visit 113 (end of the

DSP-5423P application in the cohort 1 and cohort 2 each). At other visits, blood samples should be collected under fasting conditions, whenever possible.

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. Detailed instructions regarding12-lead ECG can refer to the instructions manual provided by the Sponsor

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 metabolites [Note 1]

Note 1) metabolites to be measured
Cohort 1: M-1 (N-de-ethylated), M-2 (N-oxide), M-3 (7OH) (hydroxide), M-3 (8OH) (hydroxide), M-4 (ethylenediamine), and M-8 (carboxylic acid).
Cohort 2: M-1 (N-de-ethylated)

Recording

The following information will be recorded in the CRFs. When a subject is discontinued, the information will be recorded to CRFs according to the period of discontinuation [DSP-5423 (tablet) administration period or DSP-5423P application period].

(1) DSP-5423 (tablet) administration period:

1) Dates and times of blood sample collection
2) Dates and times of the last two administrations of DSP-5423 (tablet) before blood sample collection
3) DSP-5423 (tablet) doses of the last two administrations before blood sample collection

4) Yes or no for the question whether had a meal immediately before administrations of DSP-5423 (tablet) of the last two administrations before blood sample collection

(2) DSP-5423P application period:

1) Dates and times of blood sample collection
2) Dates and times of the last two applications of DSP-5423P before blood sample collection
3) DSP-5423P doses of the last two applications before blood sample collection
4) Locations for the last two applications of DSP-5423P before blood sample collection

Timing and volume of blood collection

Six milliliters of blood will be collected at each time point.

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).

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)

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 metabolites and prepare a bioanalysis report.

11.5 Other assessments

11.5.1 DAI-10

DAI-10's [ref 12] is an assessment for evaluating a drug adherence by adding the patient’s attitude to the drug treatment compliance. Investigator will survey the subject's drug attitude ("true" or "false") for the following 10 items and record the assessment Date and the results to CRFs.

Good things about medication outweigh the bad

1) Feel like a zombie
2) Take of my own free choice

3) Feel more relaxed
4) Feel tired and sluggish
5) Take only when sick
6) Feel more normal
7) Unnatural for my mind and body to be controlled by medications
8) Thoughts are clearer
9) By staying on medication I can prevent a breakdown

11.5.2 EQ-5D

EQ-5D's [ref 13)] is a self-administered, comprehensive rating scale developed to measure health-related quality of life. Investigator will use the questionnaire to investigate the following 5 items and record the assessment Date and the result to CRFs.

1) MOBILITY
   <1: I have no problems in walking about, 2: I have slight problems in walking about, 3: I have moderate problems in walking about, 4: I have severe problems in walking about, 5: I am unable to walk about>
2) SELF-CARE
   <1: I have no problems washing or dressing myself, 2: I have slight problems washing or dressing myself, 3: I have moderate problems washing or dressing myself, 4: I have severe problems washing or dressing myself, 5: I am unable to wash or dress myself
3) USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
   <1: I have no problems doing my usual activities, 2: I have slight problems doing my usual activities, 3: I have moderate problems doing my usual activities, 4: I have severe problems doing my usual activities, 5: I am unable to do my usual activities.
4) PAIN / DISCOMFORT
   <1: I have no pain or discomfort, 2: I have slight pain or discomfort, 3: I have moderate pain or discomfort, 4: I have severe pain or discomfort, 5: I have extreme pain or discomfort>
5) ANXIETY / DEPRESSION
   <1: I am not anxious or depressed, 2: I am slightly anxious or depressed, 3: I am moderately anxious or depressed, 4: I am severely anxious or depressed, 5: I am extremely anxious or depressed>

11.5.3 Questionnaire on dosage form

Investigator will ask Question 1 and Question 2 regarding the patch dosage form of antipsychotic, Question 3 regarding the DSP-5423P, and record the assessment Date and the results to CRFs.

- Would you like the patch dosage form to be available??

Response) "Yes" or "No"

- Is it easy for you to continue treatment with patches compared with tablets?

  Response) "Yes," "Equal" or "No."

- Question 3 Would you like to use the patches that you used during this study in the future?

  Response) "Yes" or "No"

12. SAFETY REPORTING

12.1 Definition

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 DSP-5423 (tablet) administration until the follow-up visit in the cohort 1, or from the beginning of the DSP-5423P application until the follow-up visit in the cohort 2, for instance, events occurring in association with study-related procedures or assessments, or those occurring under placebo treatment.

In the cohort 1. AEs that occur during the DSP-5423 (tablet) administration period and worsen during the DSP-5423P application period will be recorded as AEs in the DSP-5423 (tablet) administration period and also as AEs in the DSP-5423P application period. The date of worsening will be recorded as the onset date of the worsening AE. In addition, AEs that occur during the DSP-5423 (tablet) administration period without further worsening in the DSP-5423P application period will be recorded as AEs in the DSP-5423 (tablet) administration period.

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); 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 of 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:

- 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 Sponsor is the contact person. The contact information as well as other emergency contact information can be found in Table 1 Emergency Contact Information.

12.4 Immediately Reportable Events

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

- SAE
- Pregnancy

Emergency contact information can be found in Table 1 Emergency Contact Information.

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 DSP-5423 (tablet) administration until the follow-up visit in the cohort 1, or from the beginning of the DSP-5423P application until the follow-up visit in the cohort 2, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs occurring during above period must be recorded in the CRFs.

Following the end of subject participation in the study, the Investigator should report SAEs “spontaneously” to the Sponsor 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 (Table 1 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;

- History of any ADRs, relevant special conditions of the subject, history of the current disease and treatment for the disease, details of the SAE, treatment for the SAE and details on course of the SAE
- If the subject died, date of death, cause of death, relationship between the SAE and death, anatomic findings (if available)

These SAEs must be promptly reported in writing to the head of the study center by the Principal Investigator. The Principal Investigator should report available information in writing 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 will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authority in accordance with applicable law(s) and regulation(s).

12.4.2 Pregnancy

Pregnancies that occur from the beginning of the DSP-5423 (tablet) administration until the follow-up visit in the cohort 1, or from the beginning of the DSP-5423P application until the follow-up visit in the cohort 2 will be collected and reported to the Sponsor.

If a subject becomes pregnant during the above period, 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. The Investigator must complete the Pregnancy Event Form and send it to the Sponsor.

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 subjects treated with study drug prematurely discontinuing the study drug, regardless of cause, to undergo final evaluation procedures, in accordance with the discontinuation visit and the follow-up visit. Required assessment should be conducted at discontinuation visit accordance with the table 2 or 3 (DSP-5423 (tablet administration period or DSP-5423P application period). If a subject discontinues during the DSP-5423P application period, the subject will undergo all the discontinuation assessments in accordance with the discontinuation visit as described in Table 2 and 3. If a subject discontinues during the DSP-5423 (tablet) administration period, the subject will undergo the following safety assessments: study treatment compliance, DIEPSS, C-SSRS, laboratory test, pregnancy test, 12-lead ECG, body weight, body temperature, blood pressure, pulse rate, and adverse event monitoring at the discontinuation visit.

The subject will undergo the discontinuation assessments within 5 days of the last study drug

administration/application.

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. 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.

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. Statistical analysis plan

Details of the statistical methods will be specified in the statistical analysis plan. The sponsor will determine detailed data handling, including adoption or rejection for each subject to analysis populations before database hard lock. When separately analyzing the pharmacokinetics and PK-PD, the details of the analytical procedures will be specified in an analysis plan and if appropriate pooled analysis with other studies will be performed and reported separately.

15.1 Target sample size

Number of subjects enrolled: 200 subjects

- Number of subjects treated with DSP-5423P for 6 weeks and more in cohort 1: 50 subjects
- Number of subjects treated with DSP-5423P for 52 weeks in either cohort 1 or cohort 2: 100 subjects

The new enrollment can be terminated at the time when 100 subjects with 52-week exposure of DSP-5423P are collected, together with a separate confirmatory study [Confirmatory Study of DSP-5423P in Patients with Schizophrenia <Phase 3> (protocol: D4904020)].

Rationale

Based on the guideline, THE EXTENT OF POPULATION EXPOSURE TO ASSESS CLINICAL SAFETY FOR DRUGS INTENDED FOR LONG-TERM TREATMENT OF NON-LIFE-THREATENING CONDITIONS dated 24 May 1995, 100 subjects with one year (52 weeks) exposure of DSP-5423P will be collected in cohort 1 and 2. In addition, to investigate the safety and efficacy of switching DSP-5423 (tablet) to DSP-5423P, approximately half of the target number of subjects will be enrolled in cohort 1 as subjects who switched DSP-5423 (tablet) to DSP-5423P. Considering approximately half of enrolled subjects early terminated in previous studies of DSP-5423 (tablet),

target number of subjects was set to 200. No statistical consideration was applied.

15.2 Analysis population

15.2.1 Safety analysis population

Subjects with at least one application of DSP-5423P.

Efficacy analysis will also be performed based on the safety analysis population.

15.2.2 Pharmacokinetic analysis population

Subjects with at least one application of DSP-5423P, and with measurements of plasma bronanserin concentration after application of DSP-5423P.

15.3 Data Analysis

Baseline definitions are provided in 15.3.10.3.

15.3.1 Subject disposition

The following is done for each cohort.

1) Cohort 1

   Subjects with informed consent, subjects took DSP-5423 (tablet) in DSP-5423 (tablet) treatment period, subjects who didn't apply DSP-5423P in DSP-5423P application period, subjects who applied DSP-5423P in DSP-5423P application period, subjects who completed DSP-5423P application period, and subject who early terminated from DSP-5423P application period.

2) Cohort 2

   Subjects with informed consent, subjects applied DSP-5423P in DSP-5423P application period, subjects who completed DSP-5423P application period, and subject who early terminated from DSP-5423P application period.

15.3.2 Treatment exposure and Compliance

For each analysis population, perform the following for each cohort.

1) Cohort 1

   Total dose, compliance and treatment duration of DSP-5423 (tablet) administration period, and total dose, compliance and treatment duration of DSP-5423P patch period will be summarized in descriptive statistics.

2) Cohort 2

   Ttotal dose, compliance and treatment duration of DSP-5423P patch period will be summarized in descriptive statistics.

15.3.3 Important protocol deviations

Important protocol deviation (IPDs) will be confirmed after reviewing deviations as potential IPDs. The potential IPDs will be identified through programming checks of the data and reviews of the extracted data. Subjects seems have potential IPDs include, but are not limited to, the following:

- Subject who deviated inclusion/exclusion criteria
- Subject who took prohibited concomitant medication/therapy

The number and percentage of subjects with IPD will be summarized by cohort and IPDs catogory. For Cohort1, IPDs in DSP-5423(tablet) treatment period and ones in DSP-5423P application period will be summarized separately. IPDs will be listed.

15.3.4 Demographic and other reference range characteristics

Demographic and baseline characteristics will be summarized based on each analysis population for each cohort.

15.3.5 Efficacy analysis

The efficacy analysis will be performed for each cohort based on safety analysis population.

15.3.5.1 PANSS and CGI-S

Summary statistics will be calculated for the following endpoints.

1) Change from Baseline in PANSS Sum Score
2) Change in total scores by PANSS subscale from baseline
3) Change in sum scores by PANSS 5 factors model from baseline
4) Change in CGI-S scores from baseline

15.3.5.2 Time to treatment discontinuation from the initial application of DSP-5423P

Kaplan-Meier method will be applied for the analysis.

15.3.5.3 Adjusting the multiplicity

No adjustments for multiplicity are performed.

15.3.6 Safety analysis

The following safety analysis will be performed by cohorts based on safety analysis population.

15.3.6.1 Adverse event

Treatment-emergent adverse event(TEAE) will be summarized. TEAE is defined as the adverse events with start date on or after Day 1. A treatment-related TEAE is defined as a TEAE for which the causal relationship to the study treatment is either ‘definite’, ‘probable’, or ‘possible’.

The number and percentage of subjects who have TEAE or treatment-related TEAE will be

summarized. Death, Serious TEAE, TEAE leading to treatment discontinuation, severe TEAE, extrapyramidal TEAE, and skin related TEAE will be summarized in the same manner.

15.3.6.2 DIEPSS

1) Change from Baseline in DIEPSS total score (excluding overall severity)

   Summary statistics will be caluculated by visits.

2) Change from Baseline to DIEPSS item scores

   For each item score, a shift table will be created based on the baseline to the highest scores per subjects.

15.3.6.3 Laboratory test, ECGs, and vital sign

The summary statistics of measurements will be caluculated by visits.

15.3.6.4 Concomitant use of antiparkinson drug

The number and percentage of subjects with concomitant use of antiparkinson drugs in DSP-5423P application period will be summarized.

15.3.6.5 C-SSRS

The number and percentage of subjects with either suicidal ideation or suicidal behavior at least once in DSP-5423P application period will be summarized.

15.3.6.6 Skin irritation assessment

Distribution of maximum score will be presented.

15.3.7 Pharmacokinetic analysis

The summary statistics of the following variables will be provided by visits based on pharmacokinetic analysis population.

1) Plasma concentration of bronanserin
2) Plasma concentration of [Note 1)] metabolites

Note 1) metabolite of interest

Cohort 1: M-1 (N-de-ethylated), M-2 (N-oxide), M-3 (7OH) (hydroxide), M-3 (8OH) (hydroxide), M-4 (ethylenediamine), and M-8 (carboxylic acid)

Cohort 2: M-1 (N-de-ethylated)

15.3.8 Analysis of other endpoints

The following analysis will be performed based on safety analysis population.

1) DAI-10 total scores

Summary statistics will be calculated by visits.

2) EQ-5D index score

Summary statistics will be calculated by visits.

3) Questionnaire on dosage form

The number and percentage of subjects by each question will be summarized.

15.3.9 Interim analysis

Interim analysis to judge study continuation is not performed. However, for submission purpose, it might be conducted before final database lock.

15.3.10 Data handling

15.3.10.1 Day 1

Day 1 is defined as the day of the initial application of DSP-5423P for each subject.

15.3.10.2 Analysis visit

All data will be organized and analyzed according to the scheduled timing as outlined in Table 2 and 3 Schedule of Assessments and according to the visit denoted in the CRFs. Unscheduled visits may not be used for any analysis unless otherwise specified. The data collected at the discontinuation visit within 7 days from the final application of study drug are mapped to the next scheduled visit of the actual discontinuation date and utilized for analysis.

15.3.10.3 Baseline

Baseline value for analysis is defined as the last non-missing data on or prior to Day 1.

15.3.10.4 LOCF endpoint

The LOCF endpoint is defined as the last data captured on Day 1 through 7 days after the final application of DSP-5423P.

15.3.10.5 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.

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:

1) The outcome, severity, seriousness of AEs
2) Causal relationship to the study treatment
3) The reasons for concomitant use
4) The reasons for dose changing of study drugs
5) 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 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 with laboratory certification and a current, dated copy of normal range values.

17. ETHICAL AND REGULATORY OBLIGATIONS

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 the “Investigator Approval" page.

17.2 Institutional Review Board

Documented approval for conducting the study from the appropriate Institutional Review Board (IRB) 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 approval must be obtained and also forwarded to the Sponsor.

A copy of written IRB approval or a favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to the Sponsor before start of the study.

The Investigator is responsible for obtaining from the IRB 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. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform the IRB of all SAEs reported by subjects enrolled in the study or other safety information reported from the Sponsor 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 for approval before submission to the IRB. The informed consent form will be approved by the Sponsor before submission to the IRB.

The Sponsor 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 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, Emergency deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB. 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, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB 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 and the IRB 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 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. However, excluding the cases a) to d) below.

a) When the (causal) relationship between this study and the adverse event or injury is denied, it does not constitute a study subject of compensation.
b) It shall not be a study subject of compensation in the event that adverse event or injury occurs due to participating medical institution or a reason attributable to the liability of a third party.
c) If the expected effects of the drug or other benefits cannot be offered, it should not be a study subject of compensation.
d) Damage to health due to intentional or serious negligence on the part of the subject may not be compensated or may be restrict.

6) The sponsor shall take necessary measures, such as enrolling in clinical study insurance for compensation.

17.10 Payment of transportation expenses to reduce the burden associated with this study participation

In order to reduce the burden associated with this clinical study participation, the subject may be paid for transportation expenses, etc. in accordance with the rule of the site.

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19. Appendix

- Clinical study implementation system