ロナセン錠 2mg、同錠 4mg、同錠 8mg、同散 2%
製造販売承認事項一部変更承認申請
（小児用法・用量追加）
CTD 第 2 部

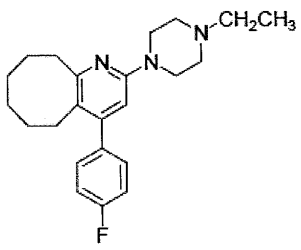
2.7　臨床概要
2.7.4　臨床的安全性の概要

大日本住友製薬株式会社

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【本項における用語の説明】

用語	定義、読み替え等
ブロナンセリン	一般名  luorophenyl)-5,6,7,8,9,10-hexahydrocycloocta
ロナセン経口剤	ブロナンセリンを含有する経口剤:ロナセン®錠 2mg、ロナセン®錠 4mg、ロナセン®錠 8mg、ロナセン®散 2%
DSP-5423	臨床試験での治験成分記号 販売名：ロナセン®錠

【一般的略号】

略号	省略しない表現	日本語
ALT	Alanine aminotransferase	アラニンアミノトランスフェラーゼ
AST	Aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
BMI	Body Mass Index	体格指数
CGI-I	Clinical Global Impressions scale-Global Improvement	–
CGI-S	Clinical Global Impressions scale-Severity of Illness	–
CGI-SS	Clinical Global Impression of Suicide Severity	–
CK	Creatine phosphokinase	クレアチンホスホキナーゼ
Cl	Chloride	クロール
DIEPSS	Drug Induced Extra-Pyramidal Symptoms Scale	薬原性錐体外路症状評価尺度
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision	精神疾患の診断と統計マニュアル第4版テキスト改訂版
γ-GTP	γ-glutamyl transpeptidase	γ-グルタミントランスペプチターゼ
HbA1c	Hemoglobin A1c	ヘモグロビン A1c
HIV	Human immunodeficiency virus	ヒト免疫不全ウイルス
HLGT	High level group term	高位グループ語（MedDRA）
HPD	–	ハロペリドール
K	Potassium	カリウム
LDH	Lactate dehydrogenase	乳酸脱水素酵素
LNS	–	ロナセン錠
LOCF	Last Observation Carried Forward	–
MedDRA	Medical dictionary for regulatory activities	ICH 国際医薬用語集
M.I.N.I.KID	MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW for Children and Adolescents	精神疾患簡易構造化面接法
Na	Sodium	ナトリウム
PANSS	Positive and Negative Syndrome Scale	陽性陰性症状評価尺度
PET	Positron emission tomography	ポジトロン断層撮影法
PT	Preferred term	基本語（MedDRA）

略号	省略しない表現	日本語
QTc	QT interval corrected for heart rate	補正 QT 間隔
QTcB	QT interval corrected for heart rate using Bazett's formula	Bazett 補正法による補正 QT 間隔
QTcF	QT interval corrected for heart rate using Fridericia's formula	Fridericia 補正法による補正 QT 間隔
RIS	–	リスペリドン
SIADH	Syndrome of inappropriate antidiuretic hormone secretion	抗利尿ホルモン不適合分泌症候群
SMQ	Standardised MedDRA Queries	MedDRA 標準検索式
SOC	System organ class	器官別大分類（MedDRA）

【その他の略号】

略号	説明
Overall	safety analysis set 全体
DB-PLCB	長期試験に移行した被験者のうち、検証試験でプラセボ群であった被験者
DB-8MG	長期試験に移行した被験者のうち、検証試験で 8 mg/日群であった被験者
DB-16MG	長期試験に移行した被験者のうち、検証試験で 16 mg/日群であった被験者
DB-Active	長期試験に移行した被験者のうち、検証試験で 8 mg/日群又は 16 mg/日群であった被験者
DB ベースライン	検証試験ベースライン：検証試験の治療期開始時（Day 1）のランダム化前のデータ
OP ベースライン	長期試験ベースライン：長期試験の Day 1 のデータ

2.7.4.1 医薬品への曝露

2.7.4.1.1 総括的安全性評価計画及び安全性試験の記述

2.7.4.1.1.1 安全性評価に用いた臨床試験

ロナセン経口剤の小児統合失調症患者での安全性は、国内第 3 相検証試験（D4907001、添付資料番号 5.3.5.1.01：以下、検証試験）及び国内長期投与試験（D4907002、添付資料番号 5.3.5.2.01：以下、長期試験）の 2 試験で評価した。

臨床試験の概要を表 2.7.4.1-1 に、概略図を図 2.7.4.1-1 に示す。検証試験では、6 週間投与したときの安全性をプラセボと比較した。長期試験は投与期間を 52 週間とし、検証試験を完了し長期試験に移行した患者を対象に長期投与時の安全性を検討した。申請時は、長期試験の中間集計結果（データカットオフ時の解析）を使用し、最終成績（最終解析）は申請後に提出することとした。データカットオフ時の解析では、長期試験の最終被験者の 24 週時の有効性及び安全性評価終了日をデータカットオフ日とし、データカットオフ日までに得られたすべてのデータを解析した。長期試験に移行した 106 名のうち投与を完了（又は中止）した 99 名のすべてのデータ、及び投与中の 7 名のデータカットオフ日までのデータが含まれた。最終解析では、投与を完了（又は中止）した 106 名のすべてのデータが含まれた。

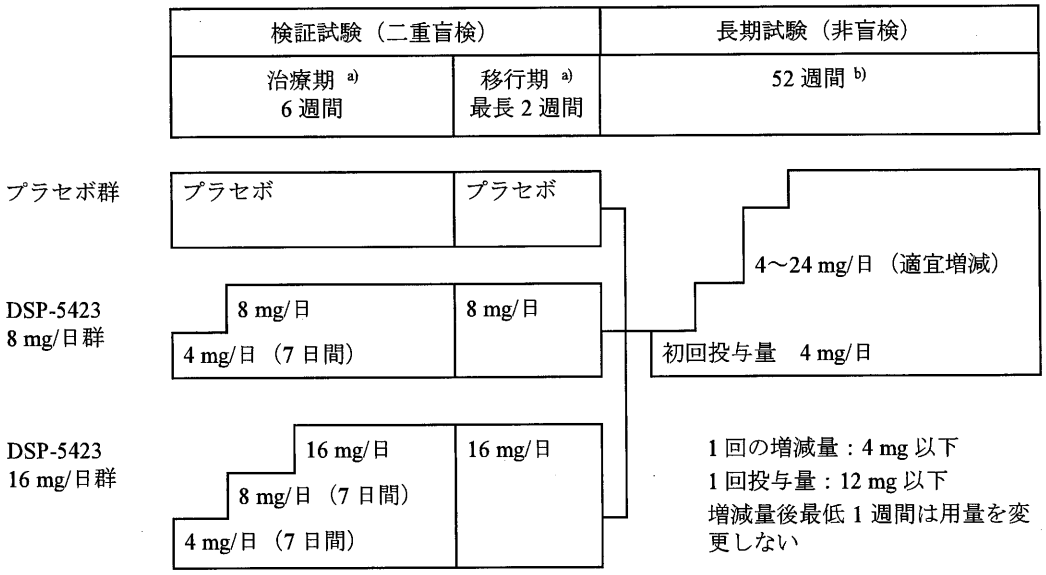
表 2.7.4.1-1 安全性を評価した臨床試験の概要

試験番号 試験略称 実施国	試験名 試験デザイン	投与期間 投与方法	投与量	安全性評価対象	資料番号
D4907001 検証試験 日本	DSP-5423 の小児統合失調症患者を対象とした検証的試験 多施設共同 プラセボ対照 ランダム化 二重盲検 並行群間比較	治療期： 6 週間 移行期： 最長 2 週間 1 日 2 回 食後 経口投与	＜8 mg/日群＞ 投与開始から 7 日間：4 mg/日 8 日目以降：8 mg/日 移行期：8 mg/日 ＜16 mg/日群＞ 投与開始から 7 日間：4 mg/日 8 日目から 7 日間：8 mg/日 15 日目以降：16 mg/日 移行期：16 mg/日 ＜プラセボ群＞ プラセボ	8 mg/日群： 51 名 16 mg/日群： 53 名 プラセボ群： 47 名 計 151 名	5.3.5.1.01
D4907002 長期試験 日本	DSP-5423 の小児統合失調症患者を対象とした長期投与試験 多施設共同 無対照 非盲検 漸増漸減	52 週間 1 日 2 回 食後 経口投与	4～24 mg/日で適宜増減 初回投与量：4 mg/日 1 回の増減量：4 mg 以下 1 回投与量：12 mg 以下 増減量後最低 1 週間は用量を変更しない	計 106 名	5.3.5.2.01

2.7.4.1.1.1.1　臨床試験の概略

検証試験及び長期試験の概略を図 2.7.4.1-1 に示す。DSP-5423 はいずれの試験でも 1 日 2 回、朝・夕食後に経口投与した。

図 2.7.4.1-1　臨床試験の概略（検証試験及び長期試験）



a) 投与を中止した被験者及び長期試験への移行を希望しなかった被験者は、最終服薬の 1～2 週後に事後観察を実施した。
b) 最終服薬の 1～4 週後に事後観察を実施した。

(1) 検証試験

治療期は 6 週間とした。8 mg/日群は DSP-5423 4 mg/日から投与を開始し、1 週間後 8 mg/日に増量した。16 mg/日群は DSP-5423 4 mg/日から投与を開始し、1 週間後に 8 mg/日に、更に 1 週間後に 16 mg/日に増量した。プラセボ群はプラセボを 6 週間投与した。移行期は最長 2 週間とし、長期試験への移行を希望する被験者は、プラセボ群にはプラセボ、8 mg/日群には 8 mg/日、16 mg/日群には 16 mg/日を盲検下で投与した。

制限した併用薬及び併用療法は 2.7.3.1.3 項に示す。

(2) 長期試験

投与期間は 52 週間とした。初回投与量は 4 mg/日とし、治験責任医師又は治験分担医師は被験者の有効性及び安全性を考慮して、4～24 mg/日の範囲で適宜増減した。増減は原則として各評価時期に行い、1 回の増減量は最大 4 mg（8 mg/日）、1 回投与量は最大 12 mg とした。増量又は減量した場合は、その後最低 1 週間は用量を変更しないこととした。1 回投与量が 12 mg 未満で、各評価時期の Clinical Global Impressions scale-Global Improvement（以下、CGI-I）が検証試験の治療期開始時と比較して改善しておらず[CGI-I が 3（Minimally improved）～7（Very much worse）]、かつ忍容性に問題がない場合、1 回 2～4 mg（4～8 mg/

日）の範囲で増量することとした。

制限した併用薬及び併用療法は 2.7.3.1.3 項に示す。

2.7.4.1.1.1.2　対象集団

検証試験及び長期試験の主な選択基準・除外基準は 2.7.3.1.1 項に示す。検証試験で対象患者の年齢は 12～18 歳とし、MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW for Children and Adolescents（以下、M.I.N.I.KID）を補助的に使用し Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision（以下、DSM-IV-TR）の診断基準に基づき統合失調症と診断された患者とした。治験開始当時のロナセン®錠の禁忌に該当する患者（昏睡状態の患者、バルビツール酸誘導体などの中枢神経抑制剤の強い影響下にある患者、アドレナリン、アゾール系抗真菌剤、HIV プロテアーゼ阻害剤を投与中の患者、ロナセン錠の成分に対し過敏症の既往歴のある患者）を除外した。また、悪性症候群、遅発性ジスキネジア、麻痺性イレウス、横紋筋融解症、無顆粒球症、肺塞栓症、深部静脈血栓症の合併又は既往歴がある患者、パーキンソン病の患者、強い自殺念慮を有する患者、自殺手段としての自傷行為、自殺企図の既往のある患者、糖尿病の患者、脱水・栄養不良状態などを伴う身体的疲弊のある患者、水中毒の合併又は既往歴がある患者、重篤な心血管系疾患、肝疾患、腎疾患、脳器質性疾患、血液疾患、内分泌疾患、痙攣性疾患などの合併症を有する患者等を除外した。なお、肝機能及び腎機能検査値に関する選択基準・除外基準は設定しなかった。

治験期間中の入院外来について、検証試験ではスクリーニング時の Clinical Global Impression of Suicide Severity（以下、CGI-SS）の重症度スコアが 2 以上の場合は 2 週時の検査・評価までは入院とし、それ以外は外来を可能とした。長期試験では治験期間を通して入院外来の規定は設けなかった。

2.7.4.1.1.1.3　解析対象集団

いずれの試験でも安全性解析対象集団（safety analysis set）を安全性評価の対象とした。安全性解析対象集団は、検証試験ではランダム化され治験期間中に 1 回以上治験薬を投与した被験者、長期試験では長期試験の治験期間中に 1 回以上治験薬を投与した被験者とした。

2.7.4.1.1.2　安全性の評価方法

2.7.4.1.1.2.1　有害事象

治験薬が投与された際に起こる（投与後新たに発現あるいは増悪した）、あらゆる好ましくない、あるいは意図しない徴候（検査値の異常変動を含む）、症状又は疾患を有害事象と定義し、治験薬との因果関係の有無は問わないこととした。検証試験では、治験薬の投与開始から移行期終了（又は事後観察期終了）までに発現したものを有害事象として収集した。長期試験では長期試験の治験薬の投与開始から事後観察期終了時までに発現したもの、

また検証試験で発現した有害事象が継続している場合は長期試験で悪化したもののみを有害事象として収集した。治験薬の有効性が認められないことも予測されるため、いずれの試験でも当該事象が通常の範囲を超えない限り有効性の欠如は有害事象としなかった。

臨床検査、体重、バイタルサイン及び12誘導心電図検査での異常値又は異常所見は治験薬の中止が必要になった場合等を有害事象とした。

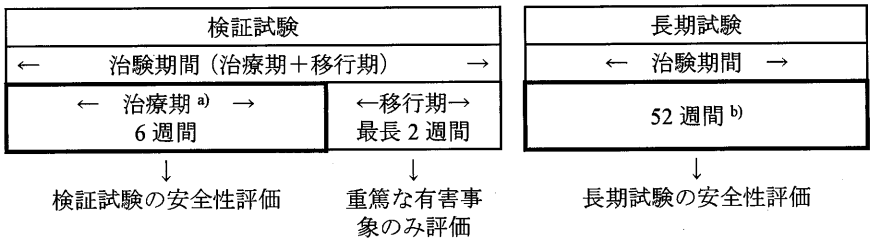
有害事象の標準化にはICH国際医薬用語集日本語版（以下、MedDRA/J）ver.21.1を用い、有害事象名は特に記載のない限りMedDRA/Jの基本語（以下、PT）を記載した。同一被験者に同一の有害事象（MedDRA/JのPTが同じ）が複数回発現した場合は1名とカウントし、重症度は最も重い評価を集計に採用した。有害事象の重症度は「軽度、中等度、重度」の3段階で判定することとした。因果関係は、「明らかに関連あり、多分関連あり、関連あるかもしれない、関連なし、判定困難」の5段階で評価することとし、治験薬との因果関係が否定できないもの（「関連なし」以外のもの）を副作用とした。

検証試験では、治療期6週間の安全性を評価した。移行期は長期試験に移行する被験者のみが対象となりランダム化された被験者と同一でないこと、最長2週間としており投与期間が一定でないことから、本項では移行期のデータを集計に含めず、治療期のみの集計を示した。また、集計には含めないが移行期に発現した重篤な有害事象を別途評価することとしたが、移行期に重篤な有害事象は発現しなかった（5.3.5.1.01参照）。

長期試験では、長期試験移行後の52週間の安全性を評価した。

有害事象を含む安全性データの評価と各試験期間の関係を図 2.7.4.1-2 に示す。検証試験と長期試験は併合解析しなかった。被験者ごとの投与期間は2.7.4.1.2項に示す。

図 2.7.4.1-2　安全性データの評価方法



a) 投与を中止した被験者及び長期試験に移行しなかった被験者の事後観察期データを含む。
b) 事後観察期データを含む。

有害事象のうち、有効成分が同一のロナセンテープ剤の医薬品リスク管理計画書（以下、RMP）の重要なリスク及びロナセン経口剤の添付文書を参考に、既存のロナセン経口剤で重要なリスクと考えられる事象に加え、小児に対して懸念される発育障害関連有害事象を注目すべき有害事象（表 2.7.4.1-2 参照）として検討した。

表 2.7.4.1-2　注目すべき有害事象

事象	定義
悪性症候群関連	悪性症候群、悪性高熱、発熱、意識変容状態、筋固縮、振戦、ジストニア、構音障害、嚥下障害、流涎過多、多汗症、頻脈、動悸、血圧変動、尿閉、ミオクローヌス、呼吸不全、ミオグロビン尿、血中クレアチンホスホキナーゼ増加、白血球数増加、横紋筋融解症、筋力低下、疲労、筋肉痛
錐体外路症状関連	錐体外路症候群（SMQ）に該当する PT 眉間反射異常、瞬目過多、流涎過多、注視麻痺、舌の麻痺、構語障害、構音障害、筋拘縮、ミオクローヌス、周期性四肢運動障害、下肢静止不能症候群、項部硬直、企図振戦
消化器系	SOC 胃腸障害に該当する PT
低ナトリウム血症及び抗利尿ホルモン不適合分泌症候群関連	低ナトリウム血症／SIADH（SMQ）に該当する PT
血液障害関連	SOC 血液およびリンパ系障害に該当する PT HLGT 血液学的検査（血液型検査を含む）に該当する PT
肺塞栓症・深部静脈血栓症関連	塞栓および血栓（SMQ）に該当する PT
肝機能障害関連	薬剤に関連する肝障害―包括的検索（SMQ）に該当する PT
耐糖能異常関連	高血糖／糖尿病の発症（SMQ）に該当する PT
自殺関連	自殺／自傷（SMQ）に該当する PT
QT/QTc 間隔延長及び催不整脈作用関連	トルサード　ド　ポアント／QT 延長（SMQ）の狭域及び広域に該当する PT 痙攣発作
中枢神経系	SOC 神経系障害に該当する PT SOC 精神障害に該当する PT
鎮静関連	昏睡、意識レベルの低下、疲労、過眠症、鎮静、傾眠、昏迷、倦怠感、鎮静合併症
転倒・外傷関連	事故および損傷（SMQ）の狭域及び広域に該当する PT
敵意・攻撃性関連	敵意／攻撃性（SMQ）に該当する PT
心血管系	SOC 心臓障害に該当する PT SOC 血管障害に該当する PT HLGT 心血管系検査（酵素検査を除く）に該当する PT
プロラクチン増加関連	無月経、無オルガズム症、血中プロラクチン、血中プロラクチン異常、血中プロラクチン増加、乳房分泌、乳房腫大、乳房痛、乳房腫脹、乳房圧痛、射精障害、乳汁漏出症、女性化乳房、男性型多毛症、高プロラクチン血症、過少月経、リビドー減退、リビドー消失、月経障害、月経遅延、不規則月経、不正子宮出血、希発月経、オルガズム異常、プロラクチン産生性下垂体腫瘍、性機能不全、オルガズム感減少、女性性機能不全、男性性機能不全、リビドー障害、勃起不全、乳汁漏出無月経症候群
体重増加関連	気晴らし食い、ボディ・マス・インデックス増加、摂食障害、脂肪組織増加、強迫的ためこみ、空腹、過食、食欲亢進、肥満、過体重、体重増加、体重変動、体重減少不良、体重管理、代謝症候群、体脂肪異常、食物渇望、代謝障害、食欲障害、摂食障害症状、ウエスト周囲径増加、中心性肥満

事象	定義
体重減少関連	脂肪組織減少、早期満腹、ボディ・マス・インデックス減少、体重減少、拒食、食欲減退、過小食、異常体重減少、過少体重、体重変動、体重増加不良、体脂肪異常、代謝障害、食欲障害、摂食障害症状、摂食障害、体重管理、栄養状態異常
脂質代謝異常関連	HLGT 脂質代謝障害に該当する PT HLGT 脂質検査に該当する PT
発育障害関連	異常体重減少、異常体重増加、血中成長ホルモン異常、血中成長ホルモン減少、血中成長ホルモン増加、ボディ・マス・インデックス減少、ボディ・マス・インデックス増加、発育遅延、低身長症、骨端閉鎖遅延、骨端早期閉鎖、成長障害、成長促進、成長ホルモン産生性下垂体腫瘍、過体重、体重減少、体重増加不良、体重増加、過少体重、体重変動、体重減少不良、成長遅延、成長ホルモン欠乏症、正常値を上回る身長、正常値を下回る身長、身長減少、身長増加、体重異常、身長異常、血中成長ホルモン放出ホルモン増加

2.7.4.1.1.2.2　臨床検査値、バイタルサイン

検証試験及び長期試験で評価した臨床検査項目を表 2.7.4.1-3 に示す。いずれの試験でも臨床検査実施機関で集中測定した。検証試験のベースライン、投与後 6 週時（又は中止時）、長期試験の投与後 52 週時（又は中止時）は空腹時採血とし、その他は可能な限り空腹時採血とした。バイタルサインとして収縮期及び拡張期血圧（坐位）、脈拍数、体温（腋窩）を評価した。臨床検査及びバイタルサインの項目ごとに定めた基準値を超えた値を顕著な異常値とし、その異常値があった被験者の割合を集計した。長期試験ではいずれの項目でもベースラインは検証試験の投与開始前値を用い、長期試験移行後の変動を評価した。

血清プロラクチン分析装置の消耗部品に不良があり、検体が所定量分注されずに測定値が実際の値よりも低値となった可能性があることが判明した。低値となっている可能性が否定できなかった検証試験の 9 測定値は信頼性が担保されないため、除外して集計することとし、除外しない集計と併せて評価した。また、これらの除外された測定値が有害事象の根拠となっていた場合でも、治験担当医師による再評価を実施せず、報告された有害事象をそのまま集計に用いることとした（5.3.5.1.01）。なお、長期試験の 24 測定値は不良部品で測定された可能性があったが、残検体を再測定した結果より 24 測定値の信頼性が担保できると申請者は判断し、24 測定値をいずれも除外しない集計で評価することとした（5.3.5.2.01）。

表 2.7.4.1-3　臨床検査項目一覧

血液学的検査	赤血球数、白血球数、血色素量、ヘマトクリット値、血小板数、白血球分画（好中球、好酸球、好塩基球、単球、リンパ球）
血液生化学的検査	AST、ALT、アルカリフォスファターゼ、γ-GTP、総蛋白、総ビリルビン、血清尿素窒素、クレアチニン、総コレステロール、トリグリセリド、LDH、CK、電解質（Na、K、Cl）、血糖、HbA1c
内分泌検査	血清プロラクチン
尿検査（定性）	定性（蛋白、糖、ウロビリノーゲン）、潜血
妊娠検査（妊娠可能な女性のみ）	尿中ヒト絨毛性ゴナドトロピン

2.7.4.1.1.2.3　体重、身長、BMI

検証試験では体重及び BMI、長期試験では身長、体重及び BMI を評価した。また、体重及び身長に対し、下記の計算式により算出した z-スコア及び国内児童の性別及び年齢ごとの分布[注)] から特定したパーセンタイルを評価した。長期試験ではいずれの項目でもベースラインは検証試験の投与開始前値を用い、長期試験移行後の変動を評価した。

z-スコア=

（被験者の測定値−該当年齢性別での平均値）/ 該当年齢性別での標準偏差 [注)]

注）国内児童の平均値、標準偏差及び分布は、文部科学省の学校保健統計調査結果（平成 29 年度）を用いた。

2.7.4.1.1.2.4　12 誘導心電図

いずれの試験でも安静時 12 誘導心電図検査を実施し、治験責任医師又は治験分担医師は心電図チャート及び心電図解析実施機関により報告された心電図パラメータ［RR 間隔、PR 間隔、QRS 幅、Bazett 補正法による補正 QT 間隔（QTcB）及び Fridericia 補正法による補正 QT 間隔（QTcF）］及び所見の結果を評価した。PR 間隔、QRS 幅、QTcB 及び QTcF は治験依頼者があらかじめ定めた基準値を超えた値を顕著な異常値とし、その異常値があった被験者の割合を集計した。心電図総括評価責任者が QTc 延長に対する影響を総合的に評価した。長期試験ではいずれの項目でもベースラインは検証試験の投与開始前値を用い、長期試験移行後の変動を評価した。

2.7.4.1.1.2.5　DIEPSS

いずれの試験でも、薬原性錐体外路症状の重症度を評価する尺度として、Drug Induced Extra-Pyramidal Symptoms Scale（以下、DIEPSS）を用いた。8 つの症状（歩行、動作緩慢、流涎、筋強剛、振戦、アカシジア、ジストニア、ジスキネジア）と概括重症度のそれぞれの項目を 0〜4 の 5 段階で評価した。DIEPSS 合計スコアは、概括重症度を除く 8 つの症状スコアの合計と定義した。

2.7.4.1.1.2.6　CGI-SS

いずれの試験でも、患者の自殺に関するリスクについて、CGI-SS [文献 1)]を用いて評価した。CGI-SS のうち、過去 7 日間の最も高かった自殺企図の状態を 1〜5 の 5 段階（低いほど軽症）でスコア化したものを重症度スコア、各評価時期のベースラインからの自殺企図の状態変化を 1〜7 の 7 段階（低いほど改善）でスコア化したものを状態変化スコアとした。CGI-SS の悪化率を、状態変化スコアで 6（Much worse）又は 7（Very much worse）になった被験者の割合と定義した。

2.7.4.1.1.2.7　抗パーキンソン薬の併用割合

抗パーキンソン薬の併用割合（治験期間中一度でも併用した被験者の割合、各時期に併用した被験者の割合）を算出した。検証試験では抗パーキンソン薬の併用は錐体外路症状が新たに発現又は増悪した場合に可とした。長期試験では、長期試験の投与開始時に抗パーキンソン薬を使用している被験者は用法・用量を変更しない場合に使用可能とし、錐体外路症状が新たに発現又は増悪した場合は、抗パーキンソン薬の新たな投与又は増量を可とした。抗パーキンソン薬の併用制限内容の詳細は 2.7.3.1.3 項に示す。

2.7.4.1.2　全般的な曝露状況

2.7.4.1.2.1　被験者の内訳

検証試験では、治験薬の投与を開始したプラセボ群 47 名、8 mg/日群 51 名、16 mg/日群 53 名が安全性解析対象集団となった。長期試験では、治験薬の投与を開始した 106 名が安全性解析対象集団となった。

検証試験及び長期試験の被験者の内訳及び中止時期別の中止理由の内訳を 2.7.3.3.1.1 項に示す。

2.7.4.1.2.2　投与期間及び曝露状況

(1) 検証試験

治療期の投与期間［Mean（SD）］は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 38.4（8.64）日、35.6（11.82）日及び 34.1（12.45）日であり、群間で大きな違いはなかった。投与期間の表を 2.7.4.7 項付録に示す。

(2) 長期試験

Overall の投与期間［Mean（SD）］は 277.2（124.94）日で、168 日（24 週）以上投与した被験者は 80 名（75.5%）、364 日（52 週）以上投与した被験者は 64 名（60.4%）であった。

最頻投与量は、4～8 mg/日が 68 名（64.2%）、10～16 mg/日が 30 名（28.3%）、18～24 mg/日が 8 名（7.5%）であった。最大投与量は、4～6 mg/日が 23 名（21.7%）、8～14 mg/日が 52 名（49.1%）、16～22 mg/日が 26 名（24.5%）、24 mg/日が 5 名（4.7%）であった。

投与期間、最頻投与量、最大投与量、平均投与量及び最終投与量の表を 2.7.3.3.1.5 項に示す。

2.7.4.1.3　治験対象集団の人口統計学的特性及びその他の特性

(1) 検証試験

安全性解析対象集団の人口統計学的特性及びその他ベースラインの特性を表 2.7.4.1-4 に、疾患データを表 2.7.4.1-5 に、抗精神病薬の前治療を表 2.7.4.1-6 に示す。

プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）で、男性の割合は 42.6%、41.2%及

び 43.4%、年齢［Mean（Min、Max）］は 15.6（13～18）歳、15.3（13～18）歳及び 15.6（12～18）歳、15 歳以上の割合は 70.2%、68.6%及び 69.8%、体重（Mean）は 52.36 kg、56.47 kg 及び 57.06 kg と、群間で大きな違いはなかった。

DSM-IV の病型は、解体型が 27.7%、5.9%及び 17.0%、緊張型が 6.4%、9.8%及び 13.2%、妄想型が 36.2%、51.0%及び 37.7%、残遺型が 0%、2.0%及び 1.9%、鑑別不能型が 29.8%、31.4%及び 30.2%で、8 mg/日群は他の群と比べて解体型が低く妄想型が高かった。エピソードの発症回数が 2 回以上は 14.9%、15.7%及び 30.2%で、罹病期間（Mean）は 2.13 年、1.98 年及び 2.55 年であった。同意取得時の入院・外来の状況は、入院が 46.8%、56.9%及び 52.8%であった。

Positive and Negative Syndrome Scale（以下、PANSS）合計スコア（Mean）は 86.5～89.8、Clinical Global Impressions scale-Severity of Illness（以下、CGI-S）スコア（Mean）は 3.94～3.98、CGI-SS 重症度スコア（Mean）は 1.06～1.13、DIEPSS 合計スコア（Mean）は 0.47～0.71 と、群間で大きな違いはなかった。

治験薬の投与開始前 28 日間に抗精神病薬の前治療があった被験者は、61.7%、58.8%及び 66.0%で、群間で大きな違いはなかった。

表 2.7.4.1-4　人口統計学的特性（検証試験）

Safety Analysis Set

	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104	Overall N = 151
Sex					
Female	27 (57.4%)	30 (58.8%)	30 (56.6%)	60 (57.7%)	87 (57.6%)
Male	20 (42.6%)	21 (41.2%)	23 (43.4%)	44 (42.3%)	64 (42.4%)
Age (years)					
n	47	51	53	104	151
Mean (SD)	15.6 (1.69)	15.3 (1.49)	15.6 (1.70)	15.5 (1.60)	15.5 (1.62)
Median	15.0	15.0	16.0	15.0	15.0
Min, Max	13, 18	13, 18	12, 18	12, 18	12, 18
Age (years)					
< 15	14 (29.8%)	16 (31.4%)	16 (30.2%)	32 (30.8%)	46 (30.5%)
>= 15	33 (70.2%)	35 (68.6%)	37 (69.8%)	72 (69.2%)	105 (69.5%)
Height (cm)					
n	47	51	53	104	151
Mean (SD)	161.09 (7.293)	160.89 (6.928)	162.83 (8.290)	161.88 (7.678)	161.64 (7.544)
Median	160.90	161.80	161.70	161.75	161.50
Min, Max	144.9, 175.7	148.0, 179.6	147.3, 181.8	147.3, 181.8	144.9, 181.8
Weight (kg)					

	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104	Overall N = 151
n	47	51	52	103	150
Mean (SD)	52.36 (7.943)	56.47 (11.951)	57.06 (11.671)	56.77 (11.756)	55.39 (10.877)
Median	51.40	53.40	54.85	54.60	53.05
Min, Max	38.0, 72.9	39.6, 89.7	39.5, 89.5	39.5, 89.7	38.0, 89.7
Weight (kg)					
< 50 kg	17 (36.2%)	17 (33.3%)	16 (30.2%)	33 (31.7%)	50 (33.1%)
>= 50 kg	30 (63.8%)	34 (66.7%)	36 (67.9%)	70 (67.3%)	100 (66.2%)
Missing	0	0	1 (1.9%)	1 (1.0%)	1 (0.7%)
BMI (kg/m2)					
n	47	51	52	103	150
Mean (SD)	20.14 (2.391)	21.74 (3.987)	21.54 (3.937)	21.64 (3.943)	21.17 (3.592)
Median	20.19	20.76	21.46	20.96	20.59
Min, Max	15.2, 25.8	15.8, 32.1	15.4, 36.5	15.4, 36.5	15.2, 36.5
DSM-IV subtype					
Disorganized	13 (27.7%)	3 (5.9%)	9 (17.0%)	12 (11.5%)	25 (16.6%)
Catatonic	3 (6.4%)	5 (9.8%)	7 (13.2%)	12 (11.5%)	15 (9.9%)
Paranoid	17 (36.2%)	26 (51.0%)	20 (37.7%)	46 (44.2%)	63 (41.7%)
Residual	0	1 (2.0%)	1 (1.9%)	2 (1.9%)	2 (1.3%)
Undifferentiated	14 (29.8%)	16 (31.4%)	16 (30.2%)	32 (30.8%)	46 (30.5%)
M.I.N.I. KID indication					
Psychotic Disorders	47 (100.0%)	51 (100.0%)	53 (100.0%)	104 (100.0%)	151 (100.0%)
Number of episodes					
1	38 (80.9%)	42 (82.4%)	36 (67.9%)	78 (75.0%)	116 (76.8%)
2	6 (12.8%)	4 (7.8%)	10 (18.9%)	14 (13.5%)	20 (13.2%)
3	0	3 (5.9%)	4 (7.5%)	7 (6.7%)	7 (4.6%)
4	0	0	2 (3.8%)	2 (1.9%)	2 (1.3%)
>= 5	1 (2.1%)	1 (2.0%)	0	1 (1.0%)	2 (1.3%)
Unknown	2 (4.3%)	1 (2.0%)	1 (1.9%)	2 (1.9%)	4 (2.6%)
Number of episodes					
1	38 (80.9%)	42 (82.4%)	36 (67.9%)	78 (75.0%)	116 (76.8%)
>= 2	7 (14.9%)	8 (15.7%)	16 (30.2%)	24 (23.1%)	31 (20.5%)
Unknown	2 (4.3%)	1 (2.0%)	1 (1.9%)	2 (1.9%)	4 (2.6%)
Hospitalization					
Inpatient	22 (46.8%)	29 (56.9%)	28 (52.8%)	57 (54.8%)	79 (52.3%)
Outpatient	25 (53.2%)	22 (43.1%)	25 (47.2%)	47 (45.2%)	72 (47.7%)

	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104	Overall N = 151
Change of hospitalization status					
No	35 (74.5%)	31 (60.8%)	38 (71.7%)	69 (66.3%)	104 (68.9%)
Yes	12 (25.5%)	20 (39.2%)	15 (28.3%)	35 (33.7%)	47 (31.1%)

- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.
- Change of hospitalization status: presence/absence of switching between inpatient/outpatient by one-month before informed consent.

表 2.7.4.1-5　疾患データ（検証試験）

Safety Analysis Set

	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104	Overall N = 151
Age at initial diagnosis (years)					
n	47	51	53	104	151
Mean (SD)	13.4 (2.21)	13.3 (2.00)	13.1 (2.19)	13.2 (2.09)	13.3 (2.13)
Median	13.0	13.0	13.0	13.0	13.0
Min, Max	9, 18	7, 16	7, 18	7, 18	7, 18
Duration of illness (years)					
n	47	51	53	104	151
Mean (SD)	2.13 (1.656)	1.98 (1.427)	2.55 (2.158)	2.27 (1.850)	2.23 (1.788)
Median	1.80	1.60	1.80	1.75	1.80
Min, Max	0.1, 7.3	0.5, 6.2	0.5, 11.9	0.5, 11.9	0.1, 11.9
Duration of current episodes (days)					
n	47	51	53	104	151
Mean (SD)	635.2 (646.32)	540.8 (493.97)	591.5 (608.10)	566.6 (552.98)	587.9 (582.32)
Median	363.0	386.0	351.0	358.0	363.0
Min, Max	6, 2667	17, 2274	16, 2519	16, 2519	6, 2667
Baseline PANSS total score					
n	47	51	52	103	150
Mean (SD)	89.8 (10.41)	86.5 (13.53)	88.7 (13.81)	87.6 (13.65)	88.3 (12.73)
Median	91.0	86.0	89.5	87.0	89.0
Min, Max	65, 111	62, 117	61, 116	61, 117	61, 117
Baseline PANSS total score					
< 80	13 (27.7%)	15 (29.4%)	13 (24.5%)	28 (26.9%)	41 (27.2%)
>= 80 to < 100	26 (55.3%)	26 (51.0%)	28 (52.8%)	54 (51.9%)	80 (53.0%)
>= 100 to <= 120	8 (17.0%)	10 (19.6%)	11 (20.8%)	21 (20.2%)	29 (19.2%)
Missing	0	0	1 (1.9%)	1 (1.0%)	1 (0.7%)

	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104	Overall N = 151
PANSS composite subscale at baseline					
Positive subscale score > Negative subscale score	15 (31.9%)	21 (41.2%)	16 (30.2%)	37 (35.6%)	52 (34.4%)
Positive subscale score = Negative subscale score	3 (6.4%)	2 (3.9%)	2 (3.8%)	4 (3.8%)	7 (4.6%)
Positive subscale score < Negative subscale score	29 (61.7%)	28 (54.9%)	34 (64.2%)	62 (59.6%)	91 (60.3%)
Missing	0	0	1 (1.9%)	1 (1.0%)	1 (0.7%)
Baseline CGI-S score					
n	47	51	52	103	150
Mean (SD)	3.98 (0.642)	3.94 (0.785)	3.98 (0.542)	3.96 (0.670)	3.97 (0.660)
Median	4.00	4.00	4.00	4.00	4.00
Min, Max	3, 5	3, 6	3, 5	3, 6	3, 6
Baseline CGI-S score					
1 - Normal, not at all ill	0	0	0	0	0
2 - Borderline mentally ill	0	0	0	0	0
3 - Mildly ill	10 (21.3%)	15 (29.4%)	8 (15.1%)	23 (22.1%)	33 (21.9%)
4 - Moderately ill	28 (59.6%)	26 (51.0%)	37 (69.8%)	63 (60.6%)	91 (60.3%)
5 - Markedly ill	9 (19.1%)	8 (15.7%)	7 (13.2%)	15 (14.4%)	24 (15.9%)
6 - Severely ill	0	2 (3.9%)	0	2 (1.9%)	2 (1.3%)
7 - Among the most extremely ill patients	0	0	0	0	0
Missing	0	0	1 (1.9%)	1 (1.0%)	1 (0.7%)
Baseline CGI-SS score					
n	47	51	52	103	150
Mean (SD)	1.13 (0.337)	1.06 (0.238)	1.08 (0.269)	1.07 (0.253)	1.09 (0.282)
Median	1.00	1.00	1.00	1.00	1.00
Min, Max	1, 2	1, 2	1, 2	1, 2	1, 2
Baseline CGI-SS score					
1 - Not at all suicidal	41 (87.2%)	48 (94.1%)	48 (90.6%)	96 (92.3%)	137 (90.7%)
2 - Mildly suicidal	6 (12.8%)	3 (5.9%)	4 (7.5%)	7 (6.7%)	13 (8.6%)
3 - Moderately suicidal	0	0	0	0	0
4 - Severely suicidal	0	0	0	0	0
5 - Attempted suicide	0	0	0	0	0
Missing	0	0	1 (1.9%)	1 (1.0%)	1 (0.7%)
Baseline DIEPSS total score					
n	47	51	52	103	150

	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104	Overall N = 151
Mean (SD)	0.47 (1.300)	0.71 (2.773)	0.56 (1.662)	0.63 (2.271)	0.58 (2.014)
Median	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 6	0, 18	0, 9	0, 18	0, 18

- PANSS positive subscale: P1 = Delusions; P2 = Conceptual disorganization; P3 = Hallucinatory behavior; P4 = Excitement; P5 = Grandiosity; P6 = Suspiciousness/persecution; P7 = Hostility.
- PANSS negative subscale: N1 = Blunted affect; N2 = Emotional withdrawal; N3 = Poor rapport; N4 = Passive/apathetic social withdrawal; N5 = Difficulty in abstract thinking; N6 = Lack of spontaneity and flow of conversation; N7 = Stereotyped thinking.
- CGI-SS score: Item score of severity of suicidality.
- DIEPSS total score: Sum of 8 item scores not including overall severity.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.1-6　抗精神病薬の前治療（検証試験）

Safety Analysis Set

Preferred name	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104	Overall N = 151
ANTIPSYCHOTICS					
Subjects with any prior medication	29 (61.7%)	30 (58.8%)	35 (66.0%)	65 (62.5%)	94 (62.3%)
RISPERIDONE	10 (21.3%)	14 (27.5%)	13 (24.5%)	27 (26.0%)	37 (24.5%)
ARIPIPRAZOLE	9 (19.1%)	11 (21.6%)	12 (22.6%)	23 (22.1%)	32 (21.2%)
OLANZAPINE	7 (14.9%)	8 (15.7%)	8 (15.1%)	16 (15.4%)	23 (15.2%)
HALOPERIDOL	4 (8.5%)	5 (9.8%)	5 (9.4%)	10 (9.6%)	14 (9.3%)
PALIPERIDONE	1 (2.1%)	4 (7.8%)	4 (7.5%)	8 (7.7%)	9 (6.0%)
QUETIAPINE FUMARATE	6 (12.8%)	4 (7.8%)	4 (7.5%)	8 (7.7%)	14 (9.3%)
SULTOPRIDE HYDROCHLORIDE	0	1 (2.0%)	3 (5.7%)	4 (3.8%)	4 (2.6%)
PEROSPIRONE HYDROCHLORIDE	2 (4.3%)	1 (2.0%)	1 (1.9%)	2 (1.9%)	4 (2.6%)
SULPIRIDE	2 (4.3%)	1 (2.0%)	1 (1.9%)	2 (1.9%)	4 (2.6%)
ASENAPINE MALEATE	0	0	1 (1.9%)	1 (1.0%)	1 (0.7%)
LEVOMEPROMAZINE MALEATE	0	1 (2.0%)	0	1 (1.0%)	1 (0.7%)
ZOTEPINE	1 (2.1%)	1 (2.0%)	0	1 (1.0%)	2 (1.3%)

- WHO Drug Dictionary Enhanced (Version September 1, 2017) was used for coding.
- Subjects with multiple occurrences of a medication in preferred name will only be counted once within each preferred name.
- Prior medications are medications that were taken any time before study drug. These are medications with a start date prior to first dose of study drug, regardless of end date.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験の安全性解析対象集団（以下、Overall）での男性の割合は 42.5%、年齢［Mean（Min、Max）］は 15.6（12～19）歳、15 歳以上の割合は 71.7%、体重（Mean）は 56.13 kg であった。

DSM-IV の病型は解体型が 12.3%、緊張型が 12.3%、妄想型が 40.6%、残遺型が 1.9%、鑑別不能型が 33.0%で、エピソードの発症回数 2 回以上の割合は 18.9%、罹病期間 (Mean) は 2.28 年であった。

DB ベースラインの PANSS 合計スコア [Mean (SD)] は 87.7 (12.35)、CGI-S スコア [Mean (SD)] は 3.99 (0.669)、CGI-SS 重症度スコア [Mean (SD)] は 1.08 (0.280)、DIEPSS 合計スコア [Mean (SD)] は 0.24 (0.962) であった。OP ベースラインの PANSS 合計スコアは 68.7 (16.01)、CGI-S スコアは 3.09 (0.822) であった。

検証試験の治験薬の投与開始前 28 日間に抗精神病薬の前治療があった被験者は 64.2%であった。

人口統計学的特性及びその他の特性、疾患データを 2.7.3.3.1.3 項に、前治療薬 (抗精神病薬) を 2.7.3.3.1.4 項に示す。

2.7.4.2 有害事象

2.7.4.2.1 有害事象の解析

(1) 検証試験

有害事象及び副作用の発現状況を表 2.7.4.2-1 に示す。プラセボ群 (47 名)、8 mg/日群 (51 名) 及び 16 mg/日群 (53 名) (以下同順) で、治療期の有害事象の発現割合 (発現被験者数) は 68.1% (32 名)、80.4% (41 名) 及び 92.5% (49 名)、副作用の発現割合は 25.5% (12 名)、54.9% (28 名) 及び 75.5% (40 名) であった。死亡した被験者はいなかった。重篤な有害事象を発現した被験者は 1 名、1 名及び 0 名で、有害事象により投与を中止した被験者は 3 名、5 名及び 6 名であった。

表 2.7.4.2-1　有害事象及び副作用の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE	32	(68.1%)	91	41	(80.4%)	161	49	(92.5%)	214	90	(86.5%)	375
Death	0			0			0			0		
Serious	1	(2.1%)	1	1	(2.0%)	1	0			1	(1.0%)	1
Leading to discontinuation	3	(6.4%)	4	5	(9.8%)	5	6	(11.3%)	8	11	(10.6%)	13
AE related to study drug	12	(25.5%)	28	28	(54.9%)	84	40	(75.5%)	128	68	(65.4%)	212
Death	0			0			0			0		
Serious	1	(2.1%)	1	1	(2.0%)	1	0			1	(1.0%)	1
Leading to discontinuation	3	(6.4%)	4	4	(7.8%)	4	5	(9.4%)	7	9	(8.7%)	11

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

有害事象及び副作用の発現状況を表 2.7.4.2-2 に示す。Overall での有害事象の発現割合（発現被験者数）は 90.6%（96 名）で、副作用は 65.1%（69 名）であった。DB-PLCB、DB-8MG、DB-16MG の順（以下同順）に、有害事象の発現割合（発現被験者数）は 91.7%（33 名）、91.9%（34 名）、87.9%（29 名）で、副作用は 66.7%（24 名）、67.6%（25 名）、60.6%（20 名）であった。

有害事象により 2 名（DB-16MG 2 名）が死亡した。治験中の死亡を含む重篤な有害事象を発現した被験者数は 17 名（8 名、5 名、4 名）であった。有害事象により、治験薬投与を中止した被験者数は 9 名（4 名、3 名、2 名）、治験薬を減量した被験者数は 24 名（12 名、7 名、5 名）、治験薬を増量した被験者数は 10 名（1 名、4 名、5 名）であった。

表 2.7.4.2-2　有害事象及び副作用の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE	33	(91.7%)	314	34	(91.9%)	234	29	(87.9%)	227	63	(90.0%)	461	96	(90.6%)	775
Death	0			0			2	(6.1%)	2	2	(2.9%)	2	2	(1.9%)	2
Serious	8	(22.2%)	9	5	(13.5%)	5	4	(12.1%)	4	9	(12.9%)	9	17	(16.0%)	18
Leading to discontinuation	4	(11.1%)	4	3	(8.1%)	4	2	(6.1%)	2	5	(7.1%)	6	9	(8.5%)	10
Leading to dose decrease	12	(33.3%)	17	7	(18.9%)	10	5	(15.2%)	5	12	(17.1%)	15	24	(22.6%)	32
Leading to dose increase	1	(2.8%)	1	4	(10.8%)	4	5	(15.2%)	8	9	(12.9%)	12	10	(9.4%)	13
AE related to study drug	24	(66.7%)	80	25	(67.6%)	65	20	(60.6%)	45	45	(64.3%)	110	69	(65.1%)	190
Death	0			0			0			0			0		
Serious	0			1	(2.7%)	1	0			1	(1.4%)	1	1	(0.9%)	1
Leading to discontinuation	0			2	(5.4%)	2	0			2	(2.9%)	2	2	(1.9%)	2
Leading to dose decrease	12	(33.3%)	17	6	(16.2%)	9	5	(15.2%)	5	11	(15.7%)	14	23	(21.7%)	31
Leading to dose increase	0			1	(2.7%)	1	2	(6.1%)	4	3	(4.3%)	5	3	(2.8%)	5

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.1　比較的よく見られる有害事象

2.7.4.2.1.1.1　主な有害事象

検証試験では実薬合計（8 mg/日群及び 16 mg/日群の併合）で 2%以上に発現した有害事象、長期試験では Overall で 2%以上に発現した有害事象を主な有害事象とした。また、主な有害事象のうち因果関係が否定されなかった事象を主な副作用とした。

(1) 検証試験

主な有害事象を表 2.7.4.2-3 に、主な副作用を表 2.7.4.2-4 に示す。

実薬合計で発現割合が 5%以上であった有害事象は、アカシジア、傾眠、高プロラクチン血症、血中プロラクチン増加、頭痛、振戦、悪心、ジストニア、統合失調症及び皮膚擦過傷で、そのうちプラセボ群と比べて 8 mg/日群及び 16 mg/日群で発現割合が高かった事象は、アカシジア、傾眠、高プロラクチン血症、血中プロラクチン増加、振戦及びジストニアであった。その発現割合はプラセボ群、8 mg/日群及び 16 mg/日群でそれぞれ、アカシジアが 4.3%、13.7%及び 32.1%、傾眠が 2.1%、15.7%及び 18.9%、高プロラクチン血症が 2.1%、9.8%及び 17.0%、血中プロラクチン増加が 2.1%、5.9%及び 13.2%、振戦が 0%、9.8%及び 9.4%、ジストニアが 0%、2.0%及び 13.2%で、振戦以外はプラセボ群、8 mg/日群、16 mg/日群の順に発現割合が高くなった。

実薬合計で発現割合が 5%以上であった副作用は、アカシジア、傾眠、高プロラクチン血症、血中プロラクチン増加、振戦、ジストニアで、その発現割合はプラセボ群、8 mg/日群及び 16 mg/日群でそれぞれ、アカシジアが 4.3%、13.7%及び 32.1%、傾眠が 2.1%、13.7%及び 17.0%、高プロラクチン血症が 2.1%、9.8%及び 17.0%、血中プロラクチン増加が 2.1%、5.9%及び 13.2%、振戦が 0%、9.8%及び 9.4%、ジストニアが 0%、2.0%及び 11.3%で、いずれもプラセボ群より 8 mg/日群及び 16 mg/日群で発現割合が高く、そのうち振戦以外はプラセボ群、8 mg/日群、16 mg/日群の順に発現割合が高くなった。

表 2.7.4.2-3　主な有害事象（実薬合計で発現割合 2%以上の有害事象）の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Common AE		24 (51.1%)	35 (68.6%)	47 (88.7%)	82 (78.8%)
Endocrine disorders	内分泌障害	1 (2.1%)	5 (9.8%)	9 (17.0%)	14 (13.5%)
Hyperprolactinaemia	高プロラクチン血症	1 (2.1%)	5 (9.8%)	9 (17.0%)	14 (13.5%)
Eye disorders	眼障害	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Oculogyric crisis	眼球回転発作	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Gastrointestinal disorders	胃腸障害	7 (14.9%)	10 (19.6%)	14 (26.4%)	24 (23.1%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Nausea	悪心	4 (8.5%)	5 (9.8%)	4 (7.5%)	9 (8.7%)
Vomiting	嘔吐	2 (4.3%)	1 (2.0%)	4 (7.5%)	5 (4.8%)
Abdominal pain	腹痛	2 (4.3%)	1 (2.0%)	3 (5.7%)	4 (3.8%)
Dental caries	齲歯	0	4 (7.8%)	0	4 (3.8%)
Salivary hypersecretion	流涎過多	0	0	4 (7.5%)	4 (3.8%)
Constipation	便秘	0	0	3 (5.7%)	3 (2.9%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	1 (2.1%)	2 (3.9%)	5 (9.4%)	7 (6.7%)
Malaise	倦怠感	0	1 (2.0%)	3 (5.7%)	4 (3.8%)
Pyrexia	発熱	1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Infections and infestations	感染症および寄生虫症	9 (19.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Nasopharyngitis	上咽頭炎	9 (19.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	5 (10.6%)	5 (9.8%)	8 (15.1%)	13 (12.5%)
Skin abrasion	皮膚擦過傷	3 (6.4%)	2 (3.9%)	4 (7.5%)	6 (5.8%)
Contusion	挫傷	2 (4.3%)	2 (3.9%)	3 (5.7%)	5 (4.8%)
Wound	創傷	0	1 (2.0%)	3 (5.7%)	4 (3.8%)
Investigations	臨床検査	1 (2.1%)	3 (5.9%)	7 (13.2%)	10 (9.6%)
Blood prolactin increased	血中プロラクチン増加	1 (2.1%)	3 (5.9%)	7 (13.2%)	10 (9.6%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Arthralgia	関節痛	1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Nervous system disorders	神経系障害	9 (19.1%)	20 (39.2%)	32 (60.4%)	52 (50.0%)
Akathisia	アカシジア	2 (4.3%)	7 (13.7%)	17 (32.1%)	24 (23.1%)
Somnolence	傾眠	1 (2.1%)	8 (15.7%)	10 (18.9%)	18 (17.3%)
Headache	頭痛	6 (12.8%)	6 (11.8%)	4 (7.5%)	10 (9.6%)
Tremor	振戦	0	5 (9.8%)	5 (9.4%)	10 (9.6%)
Dystonia	ジストニア	0	1 (2.0%)	7 (13.2%)	8 (7.7%)
Dyskinesia	ジスキネジア	0	0	3 (5.7%)	3 (2.9%)
Psychiatric disorders	精神障害	3 (6.4%)	4 (7.8%)	2 (3.8%)	6 (5.8%)
Schizophrenia	統合失調症	3 (6.4%)	4 (7.8%)	2 (3.8%)	6 (5.8%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害	1 (2.1%)	1 (2.0%)	5 (9.4%)	6 (5.8%)
Epistaxis	鼻出血	1 (2.1%)	0	3 (5.7%)	3 (2.9%)
Hyperventilation	過換気	0	1 (2.0%)	2 (3.8%)	3 (2.9%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-4　主な副作用（実薬合計で発現割合 2%以上の有害事象のうち因果関係が否定されなかった事象）の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Common AE related to study drug		10 (21.3%)	27 (52.9%)	39 (73.6%)	66 (63.5%)
Endocrine disorders	内分泌障害	1 (2.1%)	5 (9.8%)	9 (17.0%)	14 (13.5%)
Hyperprolactinaemia	高プロラクチン血症	1 (2.1%)	5 (9.8%)	9 (17.0%)	14 (13.5%)
Eye disorders	眼障害	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Oculogyric crisis	眼球回転発作	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Gastrointestinal disorders	胃腸障害	4 (8.5%)	2 (3.9%)	8 (15.1%)	10 (9.6%)
Nausea	悪心	3 (6.4%)	2 (3.9%)	2 (3.8%)	4 (3.8%)
Vomiting	嘔吐	2 (4.3%)	0	2 (3.8%)	2 (1.9%)
Abdominal pain	腹痛	0	0	1 (1.9%)	1 (1.0%)
Salivary hypersecretion	流涎過多	0	0	4 (7.5%)	4 (3.8%)
Constipation	便秘	0	0	2 (3.8%)	2 (1.9%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	1 (2.1%)	1 (2.0%)	3 (5.7%)	4 (3.8%)
Malaise	倦怠感	0	0	3 (5.7%)	3 (2.9%)
Pyrexia	発熱	1 (2.1%)	1 (2.0%)	0	1 (1.0%)
Investigations	臨床検査	1 (2.1%)	3 (5.9%)	7 (13.2%)	10 (9.6%)
Blood prolactin increased	血中プロラクチン増加	1 (2.1%)	3 (5.9%)	7 (13.2%)	10 (9.6%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	0	1 (2.0%)	0	1 (1.0%)
Arthralgia	関節痛	0	1 (2.0%)	0	1 (1.0%)
Nervous system disorders	神経系障害	4 (8.5%)	16 (31.4%)	30 (56.6%)	46 (44.2%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Akathisia	アカシジア	2 (4.3%)	7 (13.7%)	17 (32.1%)	24 (23.1%)
Somnolence	傾眠	1 (2.1%)	7 (13.7%)	9 (17.0%)	16 (15.4%)
Headache	頭痛	1 (2.1%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Tremor	振戦	0	5 (9.8%)	5 (9.4%)	10 (9.6%)
Dystonia	ジストニア	0	1 (2.0%)	6 (11.3%)	7 (6.7%)
Dyskinesia	ジスキネジア	0	0	3 (5.7%)	3 (2.9%)
Psychiatric disorders	精神障害	3 (6.4%)	3 (5.9%)	1 (1.9%)	4 (3.8%)
Schizophrenia	統合失調症	3 (6.4%)	3 (5.9%)	1 (1.9%)	4 (3.8%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害	0	1 (2.0%)	1 (1.9%)	2 (1.9%)
Epistaxis	鼻出血	0	0	1 (1.9%)	1 (1.0%)
Hyperventilation	過換気	0	1 (2.0%)	0	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

主な有害事象を表 2.7.4.2-5 に、主な副作用を表 2.7.4.2-6 に示す。

Overall で発現割合が最も高かった有害事象は上咽頭炎（35.8%）で、続いて統合失調症（19.8%）、アカシジア（17.9%）、頭痛（17.0%）、振戦（17.0%）、嘔吐（14.2%）、体重増加（14.2%）、ざ瘡（14.2%）、ジストニア（11.3%）、皮膚擦過傷（10.4%）、便秘（10.4%）が高かった。発現割合が最も高かった副作用はアカシジア（17.9%）で、続いて振戦（16.0%）、ジストニア（11.3%）、高プロラクチン血症（9.4%）、体重増加（9.4%）、血中プロラクチン増加（9.4%）、傾眠（9.4%）、便秘（5.7%）が高かった。

表 2.7.4.2-5　主な有害事象（Overall で発現割合 2%以上の有害事象）の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Blood and lymphatic system disorders	血液およびリンパ系障害					
Iron deficiency anaemia	鉄欠乏性貧血	1 (2.8%)	2 (5.4%)	0	2 (2.9%)	3 (2.8%)
Endocrine disorders	内分泌障害					
Hyperprolactinaemia	高プロラクチン血症	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Eye disorders	眼障害					
Conjunctivitis allergic	アレルギー性結膜炎	4 (11.1%)	3 (8.1%)	1 (3.0%)	4 (5.7%)	8 (7.5%)
Gastrointestinal disorders	胃腸障害					
Vomiting	嘔吐	5 (13.9%)	5 (13.5%)	5 (15.2%)	10 (14.3%)	15 (14.2%)
Constipation	便秘	4 (11.1%)	2 (5.4%)	5 (15.2%)	7 (10.0%)	11 (10.4%)
Diarrhoea	下痢	3 (8.3%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	10 (9.4%)
Abdominal pain	腹痛	5 (13.9%)	1 (2.7%)	3 (9.1%)	4 (5.7%)	9 (8.5%)
Nausea	悪心	2 (5.6%)	3 (8.1%)	4 (12.1%)	7 (10.0%)	9 (8.5%)
Dental caries	齲歯	2 (5.6%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	7 (6.6%)
Abdominal discomfort	腹部不快感	3 (8.3%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	6 (5.7%)
Stomatitis	口内炎	2 (5.6%)	0	3 (9.1%)	3 (4.3%)	5 (4.7%)
Anal fissure	裂肛	1 (2.8%)	3 (8.1%)	0	3 (4.3%)	4 (3.8%)
Toothache	歯痛	0	0	4 (12.1%)	4 (5.7%)	4 (3.8%)
Abdominal pain upper	上腹部痛	2 (5.6%)	0	1 (3.0%)	1 (1.4%)	3 (2.8%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態					

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Peripheral swelling	末梢腫脹	1 (2.8%)	2 (5.4%)	2 (6.1%)	4 (5.7%)	5 (4.7%)
Pyrexia	発熱	2 (5.6%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	4 (3.8%)
Malaise	倦怠感	3 (8.3%)	0	0	0	3 (2.8%)
Immune system disorders	免疫系障害					
Seasonal allergy	季節性アレルギー	0	2 (5.4%)	2 (6.1%)	4 (5.7%)	4 (3.8%)
Infections and infestations	感染症および寄生虫症					
Nasopharyngitis	上咽頭炎	17 (47.2%)	13 (35.1%)	8 (24.2%)	21 (30.0%)	38 (35.8%)
Bronchitis	気管支炎	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Hordeolum	麦粒腫	2 (5.6%)	0	3 (9.1%)	3 (4.3%)	5 (4.7%)
Influenza	インフルエンザ	2 (5.6%)	3 (8.1%)	0	3 (4.3%)	5 (4.7%)
Pharyngitis	咽頭炎	0	2 (5.4%)	2 (6.1%)	4 (5.7%)	4 (3.8%)
Conjunctivitis	結膜炎	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Gastroenteritis	胃腸炎	0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Otitis media	中耳炎	2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症					
Skin abrasion	皮膚擦過傷	5 (13.9%)	3 (8.1%)	3 (9.1%)	6 (8.6%)	11 (10.4%)
Wound	創傷	3 (8.3%)	0	5 (15.2%)	5 (7.1%)	8 (7.5%)
Arthropod sting	節足動物刺傷	2 (5.6%)	5 (13.5%)	0	5 (7.1%)	7 (6.6%)
Contusion	挫傷	1 (2.8%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	6 (5.7%)
Ligament sprain	靭帯捻挫	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Investigations	臨床検査					
Weight increased	体重増加	4 (11.1%)	7 (18.9%)	4 (12.1%)	11 (15.7%)	15 (14.2%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Blood prolactin increased	血中プロラクチン増加	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	2 (5.6%)	3 (8.1%)	1 (3.0%)	4 (5.7%)	6 (5.7%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害					
Back pain	背部痛	2 (5.6%)	3 (8.1%)	3 (9.1%)	6 (8.6%)	8 (7.5%)
Myalgia	筋肉痛	3 (8.3%)	5 (13.5%)	0	5 (7.1%)	8 (7.5%)
Pain in extremity	四肢痛	2 (5.6%)	2 (5.4%)	2 (6.1%)	4 (5.7%)	6 (5.7%)
Arthralgia	関節痛	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Nervous system disorders	神経系障害					
Akathisia	アカシジア	6 (16.7%)	10 (27.0%)	3 (9.1%)	13 (18.6%)	19 (17.9%)
Headache	頭痛	6 (16.7%)	7 (18.9%)	5 (15.2%)	12 (17.1%)	18 (17.0%)
Tremor	振戦	9 (25.0%)	5 (13.5%)	4 (12.1%)	9 (12.9%)	18 (17.0%)
Dystonia	ジストニア	5 (13.9%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	12 (11.3%)
Somnolence	傾眠	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Dyskinesia	ジスキネジア	2 (5.6%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	5 (4.7%)
Bradykinesia	運動緩慢	3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Dizziness	浮動性めまい	3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Psychiatric disorders	精神障害					
Schizophrenia	統合失調症	10 (27.8%)	5 (13.5%)	6 (18.2%)	11 (15.7%)	21 (19.8%)
Insomnia	不眠症	2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Intentional self-injury	故意の自傷行為	0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Reproductive system and breast disorders	生殖系および乳房障害					
Dysmenorrhoea	月経困難症	4 (11.1%)	0	1 (3.0%)	1 (1.4%)	5 (4.7%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害					
Oropharyngeal pain	口腔咽頭痛	2 (5.6%)	3 (8.1%)	4 (12.1%)	7 (10.0%)	9 (8.5%)
Epistaxis	鼻出血	1 (2.8%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	6 (5.7%)
Rhinitis allergic	アレルギー性鼻炎	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Rhinorrhoea	鼻漏	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害					
Acne	ざ瘡	8 (22.2%)	5 (13.5%)	2 (6.1%)	7 (10.0%)	15 (14.2%)
Eczema	湿疹	7 (19.4%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	10 (9.4%)
Pruritus	そう痒症	2 (5.6%)	4 (10.8%)	1 (3.0%)	5 (7.1%)	7 (6.6%)
Dermatitis contact	接触皮膚炎	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Erythema	紅斑	1 (2.8%)	0	2 (6.1%)	2 (2.9%)	3 (2.8%)
Haemorrhage subcutaneous	皮下出血	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Ingrowing nail	嵌入爪	1 (2.8%)	2 (5.4%)	0	2 (2.9%)	3 (2.8%)
Rash	発疹	2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-6　主な副作用（Overall で発現割合 2%以上の有害事象のうち因果関係が否定されなかった事象）の発現割合
（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Blood and lymphatic system disorders	血液およびリンパ系障害					
Iron deficiency anaemia	鉄欠乏性貧血	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Endocrine disorders	内分泌障害					
Hyperprolactinaemia	高プロラクチン血症	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Gastrointestinal disorders	胃腸障害					
Vomiting	嘔吐	0	2 (5.4%)	2 (6.1%)	4 (5.7%)	4 (3.8%)
Constipation	便秘	3 (8.3%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	6 (5.7%)
Diarrhoea	下痢	2 (5.6%)	0	1 (3.0%)	1 (1.4%)	3 (2.8%)
Abdominal pain	腹痛	1 (2.8%)	0	0	0	1 (0.9%)
Nausea	悪心	0	1 (2.7%)	2 (6.1%)	3 (4.3%)	3 (2.8%)
Abdominal discomfort	腹部不快感	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態					
Pyrexia	発熱	2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Malaise	倦怠感	3 (8.3%)	0	0	0	3 (2.8%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症					
Contusion	挫傷	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Investigations	臨床検査					

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Weight increased	体重増加	2 (5.6%)	4 (10.8%)	4 (12.1%)	8 (11.4%)	10 (9.4%)
Blood prolactin increased	血中プロラクチン増加	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	1 (2.8%)	0	1 (3.0%)	1 (1.4%)	2 (1.9%)
Nervous system disorders	神経系障害					
Akathisia	アカシジア	6 (16.7%)	10 (27.0%)	3 (9.1%)	13 (18.6%)	19 (17.9%)
Headache	頭痛	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Tremor	振戦	9 (25.0%)	5 (13.5%)	3 (9.1%)	8 (11.4%)	17 (16.0%)
Dystonia	ジストニア	5 (13.9%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	12 (11.3%)
Somnolence	傾眠	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Dyskinesia	ジスキネジア	2 (5.6%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	5 (4.7%)
Bradykinesia	運動緩慢	3 (8.3%)	0	0	0	3 (2.8%)
Dizziness	浮動性めまい	1 (2.8%)	0	0	0	1 (0.9%)
Psychiatric disorders	精神障害					
Schizophrenia	統合失調症	1 (2.8%)	2 (5.4%)	2 (6.1%)	4 (5.7%)	5 (4.7%)
Insomnia	不眠症	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Intentional self-injury	故意の自傷行為	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害					
Epistaxis	鼻出血	1 (2.8%)	2 (5.4%)	0	2 (2.9%)	3 (2.8%)
Rhinorrhoea	鼻漏	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害					
Acne	ざ瘡	1 (2.8%)	0	0	0	1 (0.9%)
Eczema	湿疹	1 (2.8%)	0	0	0	1 (0.9%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Pruritus	そう痒症	1 (2.8%)	0	0	0	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.1.2　重症度別

(1) 検証試験

主な有害事象の重症度別の発現割合を表 2.7.4.2-7 に示す。有害事象の多くは軽度又は中等度であった。主な有害事象のうち重度の事象として、統合失調症がプラセボ群 2 名、8 mg/日群 1 名及び 16 mg/日群 1 名、傾眠が 16 mg/日群 1 名に発現した。主な有害事象以外で重度の事象はなかった。

表 2.7.4.2-7　重症度別主な有害事象（実薬合計で 2%以上）の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Endocrine disorders	内分泌障害				
Hyperprolactinaemia	高プロラクチン血症	1 (2.1%)	5 (9.8%)	9 (17.0%)	14 (13.5%)
Mild		1 (2.1%)	5 (9.8%)	8 (15.1%)	13 (12.5%)
Moderate		0	0	1 (1.9%)	1 (1.0%)
Severe		0	0	0	0
Eye disorders	眼障害				
Oculogyric crisis	眼球回転発作	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Mild		0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Moderate		0	0	0	0
Severe		0	0	0	0
Gastrointestinal disorders	胃腸障害				
Nausea	悪心	4 (8.5%)	5 (9.8%)	4 (7.5%)	9 (8.7%)
Mild		3 (6.4%)	5 (9.8%)	3 (5.7%)	8 (7.7%)
Moderate		1 (2.1%)	0	1 (1.9%)	1 (1.0%)
Severe		0	0	0	0
Vomiting	嘔吐	2 (4.3%)	1 (2.0%)	4 (7.5%)	5 (4.8%)
Mild		2 (4.3%)	1 (2.0%)	4 (7.5%)	5 (4.8%)
Moderate		0	0	0	0
Severe		0	0	0	0

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Abdominal pain	腹痛	2 (4.3%)	1 (2.0%)	3 (5.7%)	4 (3.8%)
Mild		2 (4.3%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Moderate		0	0	1 (1.9%)	1 (1.0%)
Severe		0	0	0	0
Dental caries	齲歯	0	4 (7.8%)	0	4 (3.8%)
Mild		0	4 (7.8%)	0	4 (3.8%)
Moderate		0	0	0	0
Severe		0	0	0	0
Salivary hypersecretion	流涎過多	0	0	4 (7.5%)	4 (3.8%)
Mild		0	0	4 (7.5%)	4 (3.8%)
Moderate		0	0	0	0
Severe		0	0	0	0
Constipation	便秘	0	0	3 (5.7%)	3 (2.9%)
Mild		0	0	3 (5.7%)	3 (2.9%)
Moderate		0	0	0	0
Severe		0	0	0	0
General disorders and administration site conditions	一般・全身障害および投与部位の状態				
Malaise	倦怠感	0	1 (2.0%)	3 (5.7%)	4 (3.8%)
Mild		0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Moderate		0	0	1 (1.9%)	1 (1.0%)
Severe		0	0	0	0

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Pyrexia	発熱	1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Mild		1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Moderate		0	0	0	0
Severe		0	0	0	0
Infections and infestations	感染症および寄生虫症				
Nasopharyngitis	上咽頭炎	9 (19.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Mild		8 (17.0%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Moderate		1 (2.1%)	0	1 (1.9%)	1 (1.0%)
Severe		0	0	0	0
Injury, poisoning and procedural complications	傷害、中毒および処置合併症				
Skin abrasion	皮膚擦過傷	3 (6.4%)	2 (3.9%)	4 (7.5%)	6 (5.8%)
Mild		2 (4.3%)	2 (3.9%)	3 (5.7%)	5 (4.8%)
Moderate		1 (2.1%)	0	1 (1.9%)	1 (1.0%)
Severe		0	0	0	0
Contusion	挫傷	2 (4.3%)	2 (3.9%)	3 (5.7%)	5 (4.8%)
Mild		2 (4.3%)	2 (3.9%)	3 (5.7%)	5 (4.8%)
Moderate		0	0	0	0
Severe		0	0	0	0
Wound	創傷	0	1 (2.0%)	3 (5.7%)	4 (3.8%)
Mild		0	1 (2.0%)	3 (5.7%)	4 (3.8%)

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Moderate		0	0	0	0
Severe		0	0	0	0
Investigations	臨床検査				
Blood prolactin increased	血中プロラクチン増加	1 (2.1%)	3 (5.9%)	7 (13.2%)	10 (9.6%)
Mild		1 (2.1%)	2 (3.9%)	7 (13.2%)	9 (8.7%)
Moderate		0	1 (2.0%)	0	1 (1.0%)
Severe		0	0	0	0
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害				
Arthralgia	関節痛	1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Mild		1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Moderate		0	0	0	0
Severe		0	0	0	0
Nervous system disorders	神経系障害				
Akathisia	アカシジア	2 (4.3%)	7 (13.7%)	17 (32.1%)	24 (23.1%)
Mild		1 (2.1%)	5 (9.8%)	10 (18.9%)	15 (14.4%)
Moderate		1 (2.1%)	2 (3.9%)	7 (13.2%)	9 (8.7%)
Severe		0	0	0	0
Somnolence	傾眠	1 (2.1%)	8 (15.7%)	10 (18.9%)	18 (17.3%)
Mild		1 (2.1%)	7 (13.7%)	9 (17.0%)	16 (15.4%)
Moderate		0	1 (2.0%)	0	1 (1.0%)
Severe		0	0	1 (1.9%)	1 (1.0%)

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Headache	頭痛	6 (12.8%)	6 (11.8%)	4 (7.5%)	10 (9.6%)
Mild		5 (10.6%)	6 (11.8%)	4 (7.5%)	10 (9.6%)
Moderate		1 (2.1%)	0	0	0
Severe		0	0	0	0
Tremor	振戦	0	5 (9.8%)	5 (9.4%)	10 (9.6%)
Mild		0	4 (7.8%)	4 (7.5%)	8 (7.7%)
Moderate		0	1 (2.0%)	1 (1.9%)	2 (1.9%)
Severe		0	0	0	0
Dystonia	ジストニア	0	1 (2.0%)	7 (13.2%)	8 (7.7%)
Mild		0	0	5 (9.4%)	5 (4.8%)
Moderate		0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Severe		0	0	0	0
Dyskinesia	ジスキネジア	0	0	3 (5.7%)	3 (2.9%)
Mild		0	0	2 (3.8%)	2 (1.9%)
Moderate		0	0	1 (1.9%)	1 (1.0%)
Severe		0	0	0	0
Psychiatric disorders	精神障害				
Schizophrenia	統合失調症	3 (6.4%)	4 (7.8%)	2 (3.8%)	6 (5.8%)
Mild		1 (2.1%)	2 (3.9%)	0	2 (1.9%)
Moderate		0	1 (2.0%)	1 (1.9%)	2 (1.9%)

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Severe		2 (4.3%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害				
Epistaxis	鼻出血	1 (2.1%)	0	3 (5.7%)	3 (2.9%)
Mild		1 (2.1%)	0	2 (3.8%)	2 (1.9%)
Moderate		0	0	1 (1.9%)	1 (1.0%)
Severe		0	0	0	0
Hyperventilation	過換気	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Mild		0	0	2 (3.8%)	2 (1.9%)
Moderate		0	1 (2.0%)	0	1 (1.0%)
Severe		0	0	0	0

- Abbreviations: AE, adverse event.
- Total in row headings presents the number and proportion of subjects experiencing the event regardless of severity.
- All AEs were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a maximum severity category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

主な有害事象の重症度別の発現割合を表 2.7.4.2-8 に示す。有害事象の多くは軽度又は中等度であった。主な有害事象のうち重度の事象として、統合失調症が 6 名（5.7%）に発現した。主な有害事象以外で重度の事象は自殺既遂が 2 名（1.9%）、攻撃性、自殺企図が各 1 名（0.9%）に発現した。

表 2.7.4.2-8　重症度別主な有害事象（Overall で発現割合 2%以上の有害事象）の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Blood and lymphatic system disorders	血液およびリンパ系障害					
Iron deficiency anaemia	鉄欠乏性貧血	1 (2.8%)	2 (5.4%)	0	2 (2.9%)	3 (2.8%)
Mild		1 (2.8%)	2 (5.4%)	0	2 (2.9%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Endocrine disorders	内分泌障害					
Hyperprolactinaemia	高プロラクチン血症	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Mild		4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Eye disorders	眼障害					
Conjunctivitis allergic	アレルギー性結膜炎	4 (11.1%)	3 (8.1%)	1 (3.0%)	4 (5.7%)	8 (7.5%)
Mild		4 (11.1%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	7 (6.6%)
Moderate		0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Severe		0	0	0	0	0
Gastrointestinal disorders	胃腸障害					
Vomiting	嘔吐	5 (13.9%)	5 (13.5%)	5 (15.2%)	10 (14.3%)	15 (14.2%)
Mild		5 (13.9%)	5 (13.5%)	5 (15.2%)	10 (14.3%)	15 (14.2%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Constipation	便秘	4 (11.1%)	2 (5.4%)	5 (15.2%)	7 (10.0%)	11 (10.4%)
Mild		4 (11.1%)	2 (5.4%)	5 (15.2%)	7 (10.0%)	11 (10.4%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Diarrhoea	下痢	3 (8.3%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	10 (9.4%)
Mild		3 (8.3%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	10 (9.4%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Abdominal pain	腹痛	5 (13.9%)	1 (2.7%)	3 (9.1%)	4 (5.7%)	9 (8.5%)
Mild		5 (13.9%)	1 (2.7%)	3 (9.1%)	4 (5.7%)	9 (8.5%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Nausea	悪心	2 (5.6%)	3 (8.1%)	4 (12.1%)	7 (10.0%)	9 (8.5%)
Mild		2 (5.6%)	3 (8.1%)	4 (12.1%)	7 (10.0%)	9 (8.5%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Dental caries	齲歯	2 (5.6%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	7 (6.6%)
Mild		2 (5.6%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	7 (6.6%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Abdominal discomfort	腹部不快感	3 (8.3%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	6 (5.7%)
Mild		3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Moderate		0	1 (2.7%)	1 (3.0%)	2 (2.9%)	2 (1.9%)

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Severe		0	0	0	0	0
Stomatitis	口内炎	2 (5.6%)	0	3 (9.1%)	3 (4.3%)	5 (4.7%)
Mild		2 (5.6%)	0	3 (9.1%)	3 (4.3%)	5 (4.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Anal fissure	裂肛	1 (2.8%)	3 (8.1%)	0	3 (4.3%)	4 (3.8%)
Mild		1 (2.8%)	3 (8.1%)	0	3 (4.3%)	4 (3.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Toothache	歯痛	0	0	4 (12.1%)	4 (5.7%)	4 (3.8%)
Mild		0	0	4 (12.1%)	4 (5.7%)	4 (3.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Abdominal pain upper	上腹部痛	2 (5.6%)	0	1 (3.0%)	1 (1.4%)	3 (2.8%)
Mild		2 (5.6%)	0	1 (3.0%)	1 (1.4%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
General disorders and administration site conditions	一般・全身障害および投与部位の状態					
Peripheral swelling	末梢腫脹	1 (2.8%)	2 (5.4%)	2 (6.1%)	4 (5.7%)	5 (4.7%)
Mild		1 (2.8%)	2 (5.4%)	2 (6.1%)	4 (5.7%)	5 (4.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Pyrexia	発熱	2 (5.6%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	4 (3.8%)
Mild		2 (5.6%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	4 (3.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Malaise	倦怠感	3 (8.3%)	0	0	0	3 (2.8%)
Mild		2 (5.6%)	0	0	0	2 (1.9%)
Moderate		1 (2.8%)	0	0	0	1 (0.9%)
Severe		0	0	0	0	0
Immune system disorders	免疫系障害					
Seasonal allergy	季節性アレルギー	0	2 (5.4%)	2 (6.1%)	4 (5.7%)	4 (3.8%)
Mild		0	2 (5.4%)	2 (6.1%)	4 (5.7%)	4 (3.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Infections and infestations	感染症および寄生虫症					
Nasopharyngitis	上咽頭炎	17 (47.2%)	13 (35.1%)	8 (24.2%)	21 (30.0%)	38 (35.8%)
Mild		15 (41.7%)	12 (32.4%)	8 (24.2%)	20 (28.6%)	35 (33.0%)
Moderate		2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Severe		0	0	0	0	0
Bronchitis	気管支炎	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Mild		2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Hordeolum	麦粒腫	2 (5.6%)	0	3 (9.1%)	3 (4.3%)	5 (4.7%)
Mild		1 (2.8%)	0	3 (9.1%)	3 (4.3%)	4 (3.8%)
Moderate		1 (2.8%)	0	0	0	1 (0.9%)
Severe		0	0	0	0	0
Influenza	インフルエンザ	2 (5.6%)	3 (8.1%)	0	3 (4.3%)	5 (4.7%)
Mild		2 (5.6%)	2 (5.4%)	0	2 (2.9%)	4 (3.8%)
Moderate		0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Severe		0	0	0	0	0
Pharyngitis	咽頭炎	0	2 (5.4%)	2 (6.1%)	4 (5.7%)	4 (3.8%)
Mild		0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Moderate		0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Severe		0	0	0	0	0
Conjunctivitis	結膜炎	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Mild		1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Gastroenteritis	胃腸炎	0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Mild		0	1 (2.7%)	1 (3.0%)	2 (2.9%)	2 (1.9%)
Moderate		0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Severe		0	0	0	0	0
Otitis media	中耳炎	2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Mild		2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Injury, poisoning and procedural complications	傷害、中毒および処置合併症					
Skin abrasion	皮膚擦過傷	5 (13.9%)	3 (8.1%)	3 (9.1%)	6 (8.6%)	11 (10.4%)
Mild		5 (13.9%)	3 (8.1%)	3 (9.1%)	6 (8.6%)	11 (10.4%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Wound	創傷	3 (8.3%)	0	5 (15.2%)	5 (7.1%)	8 (7.5%)
Mild		2 (5.6%)	0	5 (15.2%)	5 (7.1%)	7 (6.6%)
Moderate		1 (2.8%)	0	0	0	1 (0.9%)
Severe		0	0	0	0	0
Arthropod sting	節足動物刺傷	2 (5.6%)	5 (13.5%)	0	5 (7.1%)	7 (6.6%)
Mild		2 (5.6%)	5 (13.5%)	0	5 (7.1%)	7 (6.6%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Contusion	挫傷	1 (2.8%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	6 (5.7%)
Mild		1 (2.8%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	6 (5.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Ligament sprain	靭帯捻挫	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Mild		2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Investigations	臨床検査					

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Weight increased	体重増加	4 (11.1%)	7 (18.9%)	4 (12.1%)	11 (15.7%)	15 (14.2%)
Mild		4 (11.1%)	7 (18.9%)	4 (12.1%)	11 (15.7%)	15 (14.2%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Blood prolactin increased	血中プロラクチン増加	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Mild		4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	2 (5.6%)	3 (8.1%)	1 (3.0%)	4 (5.7%)	6 (5.7%)
Mild		2 (5.6%)	3 (8.1%)	1 (3.0%)	4 (5.7%)	6 (5.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害					
Back pain	背部痛	2 (5.6%)	3 (8.1%)	3 (9.1%)	6 (8.6%)	8 (7.5%)
Mild		2 (5.6%)	3 (8.1%)	3 (9.1%)	6 (8.6%)	8 (7.5%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Myalgia	筋肉痛	3 (8.3%)	5 (13.5%)	0	5 (7.1%)	8 (7.5%)
Mild		3 (8.3%)	5 (13.5%)	0	5 (7.1%)	8 (7.5%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Pain in extremity	四肢痛	2 (5.6%)	2 (5.4%)	2 (6.1%)	4 (5.7%)	6 (5.7%)

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Mild		2 (5.6%)	2 (5.4%)	2 (6.1%)	4 (5.7%)	6 (5.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Arthralgia	関節痛	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Mild		1 (2.8%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	4 (3.8%)
Moderate		1 (2.8%)	0	0	0	1 (0.9%)
Severe		0	0	0	0	0
Nervous system disorders	神経系障害					
Akathisia	アカシジア	6 (16.7%)	10 (27.0%)	3 (9.1%)	13 (18.6%)	19 (17.9%)
Mild		6 (16.7%)	9 (24.3%)	2 (6.1%)	11 (15.7%)	17 (16.0%)
Moderate		0	1 (2.7%)	1 (3.0%)	2 (2.9%)	2 (1.9%)
Severe		0	0	0	0	0
Headache	頭痛	6 (16.7%)	7 (18.9%)	5 (15.2%)	12 (17.1%)	18 (17.0%)
Mild		6 (16.7%)	6 (16.2%)	4 (12.1%)	10 (14.3%)	16 (15.1%)
Moderate		0	1 (2.7%)	1 (3.0%)	2 (2.9%)	2 (1.9%)
Severe		0	0	0	0	0
Tremor	振戦	9 (25.0%)	5 (13.5%)	4 (12.1%)	9 (12.9%)	18 (17.0%)
Mild		8 (22.2%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	15 (14.2%)
Moderate		1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Severe		0	0	0	0	0
Dystonia	ジストニア	5 (13.9%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	12 (11.3%)
Mild		4 (11.1%)	3 (8.1%)	1 (3.0%)	4 (5.7%)	8 (7.5%)
Moderate		1 (2.8%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	4 (3.8%)

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Severe		0	0	0	0	0
Somnolence	傾眠	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Mild		4 (11.1%)	4 (10.8%)	1 (3.0%)	5 (7.1%)	9 (8.5%)
Moderate		0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Severe		0	0	0	0	0
Dyskinesia	ジスキネジア	2 (5.6%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	5 (4.7%)
Mild		2 (5.6%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	5 (4.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Bradykinesia	運動緩慢	3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Mild		3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Dizziness	浮動性めまい	3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Mild		3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Psychiatric disorders	精神障害					
Schizophrenia	統合失調症	10 (27.8%)	5 (13.5%)	6 (18.2%)	11 (15.7%)	21 (19.8%)
Mild		1 (2.8%)	1 (2.7%)	3 (9.1%)	4 (5.7%)	5 (4.7%)
Moderate		6 (16.7%)	1 (2.7%)	3 (9.1%)	4 (5.7%)	10 (9.4%)
Severe		3 (8.3%)	3 (8.1%)	0	3 (4.3%)	6 (5.7%)

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Insomnia	不眠症	2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Mild		1 (2.8%)	1 (2.7%)	0	1 (1.4%)	2 (1.9%)
Moderate		1 (2.8%)	0	0	0	1 (0.9%)
Severe		0	0	0	0	0
Intentional self-injury	故意の自傷行為	0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Mild		0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Reproductive system and breast disorders	生殖系および乳房障害					
Dysmenorrhoea	月経困難症	4 (11.1%)	0	1 (3.0%)	1 (1.4%)	5 (4.7%)
Mild		4 (11.1%)	0	1 (3.0%)	1 (1.4%)	5 (4.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害					
Oropharyngeal pain	口腔咽頭痛	2 (5.6%)	3 (8.1%)	4 (12.1%)	7 (10.0%)	9 (8.5%)
Mild		2 (5.6%)	3 (8.1%)	4 (12.1%)	7 (10.0%)	9 (8.5%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Epistaxis	鼻出血	1 (2.8%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	6 (5.7%)
Mild		1 (2.8%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	6 (5.7%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Rhinitis allergic	アレルギー性鼻炎	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Mild		2 (5.6%)	0	2 (6.1%)	2 (2.9%)	4 (3.8%)
Moderate		0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Severe		0	0	0	0	0
Rhinorrhoea	鼻漏	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Mild		1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害					
Acne	ざ瘡	8 (22.2%)	5 (13.5%)	2 (6.1%)	7 (10.0%)	15 (14.2%)
Mild		8 (22.2%)	5 (13.5%)	2 (6.1%)	7 (10.0%)	15 (14.2%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Eczema	湿疹	7 (19.4%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	10 (9.4%)
Mild		7 (19.4%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	10 (9.4%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Pruritus	そう痒症	2 (5.6%)	4 (10.8%)	1 (3.0%)	5 (7.1%)	7 (6.6%)
Mild		2 (5.6%)	4 (10.8%)	1 (3.0%)	5 (7.1%)	7 (6.6%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Dermatitis contact	接触皮膚炎	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Mild		1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)

System Organ Class Preferred Term Severity	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Erythema	紅斑	1 (2.8%)	0	2 (6.1%)	2 (2.9%)	3 (2.8%)
Mild		1 (2.8%)	0	2 (6.1%)	2 (2.9%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Haemorrhage subcutaneous	皮下出血	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Mild		1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Ingrowing nail	嵌入爪	1 (2.8%)	2 (5.4%)	0	2 (2.9%)	3 (2.8%)
Mild		1 (2.8%)	2 (5.4%)	0	2 (2.9%)	3 (2.8%)
Moderate		0	0	0	0	0
Severe		0	0	0	0	0
Rash	発疹	2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Mild		2 (5.6%)	0	0	0	2 (1.9%)
Moderate		0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Severe		0	0	0	0	0

- Total in row headings presents the number and proportion of subjects experiencing the event regardless of severity.
- All AEs were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a maximum severity category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.1.3　初回発現時期別

(1) 検証試験

有害事象の初回発現時期を Day 1～7、Day 8～14、Day 15～28、Day 29～42、Day 43 以降で区分した。主な有害事象の初回発現時期別の発現割合を表 2.7.4.2-9 に示す。なお、DSP-5423 の投与量は 8 mg/日群及び 16 mg/日群のいずれでも 4 mg/日から開始し、1 週間後（Day 8）に 8 mg/日に増量した。16 mg/日群は更に 1 週間後（Day 15）に 16 mg/日に増量した。

治療期の Day 29 以降になんらかの有害事象を初回発現した被験者は少なかった。

事象別では、アカシジアを Day 1～7 に初回発現した被験者は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）で 1 名、2 名及び 1 名、Day 8～14 は 1 名、3 名及び 4 名、Day 15～28 は 0 名、2 名及び 11 名、Day 29～42 は 0 名、0 名及び 1 名で、Day 43 以降はいなかった。アカシジアの初回発現時期は 8 mg/日群及び 16 mg/日群のほとんどで Day 28 までであり、4 mg/日を投与した Day 1～7 よりも 8 mg/日に増量した Day 8～14 にアカシジアを初回発現した被験者が多く、16 mg/日群では更に 16 mg/ 日に増量した Day 15 以降に多かった。その他、発現割合の高かった有害事象（実薬合計で発現割合 5%以上）のうち、振戦は 8 mg/日群で Day 28 まで、16 mg/日群で Day 15～28 の初回発現が多く、ジストニアは 16 mg/日群では Day 15～28 の初回発現が多かった。高プロラクチン血症及び血中プロラクチン増加は 8 mg/日群及び 16 mg/日群のいずれでも Day 29 以降の初回発現はなく、8 mg/日群では Day 8～14 のみ、16 mg/日群では Day 8～14 の初回発現が多く Day 15～28 にも初回発現がみられた。傾眠は 8 mg/日群で Day 1～7 又は Day 15～28、16 mg/日群で Day 1～7 又は Day 8～14 の初回発現が多かった。振戦、ジストニア、高プロラクチン血症及び血中プロラクチン増加、傾眠は Day 28 までの発現が多かったが明らかな特徴はみられなかった。その他の有害事象では初回発現時期に明確な特徴はみられなかった。

表 2.7.4.2-9　初回発現時期別主な有害事象（実薬合計で発現割合 2%以上）の発現割合（検証試験、治療期）

Safety Analysis Set
PLCB, N = 47

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 47	Day 8 to 14 n = 46	Day 15 to 28 n = 45	Day 29 to 42 n = 41	Later than Day 42 n = 36	Total n = 47
Subjects with any Common AE		10 (21.3%)	6 (13.0%)	5 (11.1%)	3 (7.3%)	0	24 (51.1%)
Endocrine disorders	内分泌障害	1 (2.1%)	0	0	0	0	1 (2.1%)
Hyperprolactinaemia	高プロラクチン血症	1 (2.1%)	0	0	0	0	1 (2.1%)
Gastrointestinal disorders	胃腸障害	1 (2.1%)	4 (8.7%)	1 (2.2%)	1 (2.4%)	0	7 (14.9%)
Nausea	悪心	0	2 (4.3%)	1 (2.2%)	1 (2.4%)	0	4 (8.5%)
Vomiting	嘔吐	1 (2.1%)	0	0	1 (2.4%)	0	2 (4.3%)
Abdominal pain	腹痛	0	2 (4.3%)	0	0	0	2 (4.3%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	0	1 (2.2%)	0	0	0	1 (2.1%)
Pyrexia	発熱	0	1 (2.2%)	0	0	0	1 (2.1%)
Infections and infestations	感染症および寄生虫症	3 (6.4%)	1 (2.2%)	3 (6.7%)	2 (4.9%)	0	9 (19.1%)
Nasopharyngitis	上咽頭炎	3 (6.4%)	1 (2.2%)	3 (6.7%)	2 (4.9%)	0	9 (19.1%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	1 (2.1%)	1 (2.2%)	2 (4.4%)	1 (2.4%)	0	5 (10.6%)
Skin abrasion	皮膚擦過傷	1 (2.1%)	1 (2.2%)	1 (2.2%)	0	0	3 (6.4%)
Contusion	挫傷	0	0	1 (2.2%)	1 (2.4%)	0	2 (4.3%)
Investigations	臨床検査	0	0	0	1 (2.4%)	0	1 (2.1%)

PLCB, N = 47

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 47	Day 8 to 14 n = 46	Day 15 to 28 n = 45	Day 29 to 42 n = 41	Later than Day 42 n = 36	Total n = 47
Blood prolactin increased	血中プロラクチン増加	0	0	0	1 (2.4%)	0	1 (2.1%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	1 (2.1%)	0	0	0	0	1 (2.1%)
Arthralgia	関節痛	1 (2.1%)	0	0	0	0	1 (2.1%)
Nervous system disorders	神経系障害	4 (8.5%)	2 (4.3%)	2 (4.4%)	1 (2.4%)	0	9 (19.1%)
Akathisia	アカシジア	1 (2.1%)	1 (2.2%)	0	0	0	2 (4.3%)
Somnolence	傾眠	1 (2.1%)	0	0	0	0	1 (2.1%)
Headache	頭痛	2 (4.3%)	1 (2.2%)	2 (4.4%)	1 (2.4%)	0	6 (12.8%)
Psychiatric disorders	精神障害	0	2 (4.3%)	1 (2.2%)	0	0	3 (6.4%)
Schizophrenia	統合失調症	0	2 (4.3%)	1 (2.2%)	0	0	3 (6.4%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害	1 (2.1%)	0	0	0	0	1 (2.1%)
Epistaxis	鼻出血	1 (2.1%)	0	0	0	0	1 (2.1%)

8 MG, N = 51

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 51	Day 8 to 14 n = 49	Day 15 to 28 n = 46	Day 29 to 42 n = 39	Later than Day 42 n = 38	Total n = 51
Subjects with any Common AE		13 (25.5%)	16 (32.7%)	4 (8.7%)	2 (5.1%)	0	35 (68.6%)
Endocrine disorders	内分泌障害	0	5 (10.2%)	0	0	0	5 (9.8%)

8 MG, N = 51

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 51	Day 8 to 14 n = 49	Day 15 to 28 n = 46	Day 29 to 42 n = 39	Later than Day 42 n = 38	Total n = 51
Hyperprolactinaemia	高プロラクチン血症	0	5 (10.2%)	0	0	0	5 (9.8%)
Eye disorders	眼障害	0	1 (2.0%)	0	0	0	1 (2.0%)
Oculogyric crisis	眼球回転発作	0	1 (2.0%)	0	0	0	1 (2.0%)
Gastrointestinal disorders	胃腸障害	0	4 (8.2%)	2 (4.3%)	3 (7.7%)	1 (2.6%)	10 (19.6%)
Nausea	悪心	0	2 (4.1%)	2 (4.3%)	0	1 (2.6%)	5 (9.8%)
Vomiting	嘔吐	0	0	0	1 (2.6%)	0	1 (2.0%)
Abdominal pain	腹痛	0	0	0	1 (2.6%)	0	1 (2.0%)
Dental caries	齲歯	0	2 (4.1%)	0	2 (5.1%)	0	4 (7.8%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	1 (2.0%)	1 (2.0%)	0	0	0	2 (3.9%)
Malaise	倦怠感	0	1 (2.0%)	0	0	0	1 (2.0%)
Pyrexia	発熱	1 (2.0%)	0	0	0	0	1 (2.0%)
Infections and infestations	感染症および寄生虫症	0	0	0	1 (2.6%)	0	1 (2.0%)
Nasopharyngitis	上咽頭炎	0	0	0	1 (2.6%)	0	1 (2.0%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	2 (3.9%)	2 (4.1%)	0	1 (2.6%)	0	5 (9.8%)
Skin abrasion	皮膚擦過傷	1 (2.0%)	1 (2.0%)	0	0	0	2 (3.9%)
Contusion	挫傷	0	1 (2.0%)	0	1 (2.6%)	0	2 (3.9%)
Wound	創傷	1 (2.0%)	0	0	0	0	1 (2.0%)

8 MG, N = 51

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 51	Day 8 to 14 n = 49	Day 15 to 28 n = 46	Day 29 to 42 n = 39	Later than Day 42 n = 38	Total n = 51
Investigations	臨床検査	0	3 (6.1%)	0	0	0	3 (5.9%)
Blood prolactin increased	血中プロラクチン増加	0	3 (6.1%)	0	0	0	3 (5.9%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	0	0	0	1 (2.6%)	0	1 (2.0%)
Arthralgia	関節痛	0	0	0	1 (2.6%)	0	1 (2.0%)
Nervous system disorders	神経系障害	10 (19.6%)	4 (8.2%)	5 (10.9%)	1 (2.6%)	0	20 (39.2%)
Akathisia	アカシジア	2 (3.9%)	3 (6.1%)	2 (4.3%)	0	0	7 (13.7%)
Somnolence	傾眠	5 (9.8%)	0	2 (4.3%)	0	1 (2.6%)	8 (15.7%)
Headache	頭痛	3 (5.9%)	0	2 (4.3%)	1 (2.6%)	0	6 (11.8%)
Tremor	振戦	2 (3.9%)	1 (2.0%)	2 (4.3%)	0	0	5 (9.8%)
Dystonia	ジストニア	0	1 (2.0%)	0	0	0	1 (2.0%)
Psychiatric disorders	精神障害	1 (2.0%)	1 (2.0%)	1 (2.2%)	1 (2.6%)	0	4 (7.8%)
Schizophrenia	統合失調症	1 (2.0%)	1 (2.0%)	1 (2.2%)	1 (2.6%)	0	4 (7.8%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害	1 (2.0%)	0	0	0	0	1 (2.0%)
Hyperventilation	過換気	1 (2.0%)	0	0	0	0	1 (2.0%)

16 MG, N = 53

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 53	Day 8 to 14 n = 50	Day 15 to 28 n = 47	Day 29 to 42 n = 39	Later than Day 42 n = 33	Total n = 53
Subjects with any Common AE		13 (24.5%)	15 (30.0%)	16 (34.0%)	3 (7.7%)	0	47 (88.7%)
Endocrine disorders	内分泌障害	1 (1.9%)	7 (14.0%)	1 (2.1%)	0	0	9 (17.0%)
Hyperprolactinaemia	高プロラクチン血症	1 (1.9%)	7 (14.0%)	1 (2.1%)	0	0	9 (17.0%)
Eye disorders	眼障害	0	1 (2.0%)	0	1 (2.6%)	0	2 (3.8%)
Oculogyric crisis	眼球回転発作	0	1 (2.0%)	0	1 (2.6%)	0	2 (3.8%)
Gastrointestinal disorders	胃腸障害	3 (5.7%)	2 (4.0%)	6 (12.8%)	3 (7.7%)	0	14 (26.4%)
Nausea	悪心	0	0	4 (8.5%)	0	0	4 (7.5%)
Vomiting	嘔吐	2 (3.8%)	0	1 (2.1%)	1 (2.6%)	0	4 (7.5%)
Abdominal pain	腹痛	0	1 (2.0%)	1 (2.1%)	1 (2.6%)	0	3 (5.7%)
Salivary hypersecretion	流涎過多	0	1 (2.0%)	3 (6.4%)	0	0	4 (7.5%)
Constipation	便秘	1 (1.9%)	0	1 (2.1%)	1 (2.6%)	0	3 (5.7%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	1 (1.9%)	3 (6.0%)	0	1 (2.6%)	0	5 (9.4%)
Malaise	倦怠感	1 (1.9%)	2 (4.0%)	0	0	0	3 (5.7%)
Pyrexia	発熱	0	1 (2.0%)	0	1 (2.6%)	0	2 (3.8%)
Infections and infestations	感染症および寄生虫症	0	0	1 (2.1%)	1 (2.6%)	0	2 (3.8%)
Nasopharyngitis	上咽頭炎	0	0	1 (2.1%)	1 (2.6%)	0	2 (3.8%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	4 (7.5%)	0	3 (6.4%)	1 (2.6%)	0	8 (15.1%)

16 MG, N = 53

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 53	Day 8 to 14 n = 50	Day 15 to 28 n = 47	Day 29 to 42 n = 39	Later than Day 42 n = 33	Total n = 53
Skin abrasion	皮膚擦過傷	2 (3.8%)	0	1 (2.1%)	1 (2.6%)	0	4 (7.5%)
Contusion	挫傷	1 (1.9%)	0	1 (2.1%)	1 (2.6%)	0	3 (5.7%)
Wound	創傷	1 (1.9%)	0	1 (2.1%)	1 (2.6%)	0	3 (5.7%)
Investigations	臨床検査	0	4 (8.0%)	3 (6.4%)	0	0	7 (13.2%)
Blood prolactin increased	血中プロラクチン増加	0	4 (8.0%)	3 (6.4%)	0	0	7 (13.2%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	0	0	2 (4.3%)	0	0	2 (3.8%)
Arthralgia	関節痛	0	0	2 (4.3%)	0	0	2 (3.8%)
Nervous system disorders	神経系障害	6 (11.3%)	9 (18.0%)	17 (36.2%)	0	0	32 (60.4%)
Akathisia	アカシジア	1 (1.9%)	4 (8.0%)	11 (23.4%)	1 (2.6%)	0	17 (32.1%)
Somnolence	傾眠	3 (5.7%)	6 (12.0%)	0	0	1 (3.0%)	10 (18.9%)
Headache	頭痛	1 (1.9%)	1 (2.0%)	2 (4.3%)	0	0	4 (7.5%)
Tremor	振戦	0	1 (2.0%)	3 (6.4%)	1 (2.6%)	0	5 (9.4%)
Dystonia	ジストニア	1 (1.9%)	1 (2.0%)	4 (8.5%)	1 (2.6%)	0	7 (13.2%)
Dyskinesia	ジスキネジア	0	1 (2.0%)	1 (2.1%)	1 (2.6%)	0	3 (5.7%)
Psychiatric disorders	精神障害	1 (1.9%)	1 (2.0%)	0	0	0	2 (3.8%)
Schizophrenia	統合失調症	1 (1.9%)	1 (2.0%)	0	0	0	2 (3.8%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害	1 (1.9%)	0	2 (4.3%)	2 (5.1%)	0	5 (9.4%)
Epistaxis	鼻出血	0	0	1 (2.1%)	2 (5.1%)	0	3 (5.7%)

16 MG, N = 53

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 53	Day 8 to 14 n = 50	Day 15 to 28 n = 47	Day 29 to 42 n = 39	Later than Day 42 n = 33	Total n = 53
Hyperventilation	過換気	1 (1.9%)	0	1 (2.1%)	0	0	2 (3.8%)

- Abbreviations: AE, adverse event.
- Adverse events are defined as adverse events with a start date on or after the date of first dose through 1 day before start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- For each subject, an AE is mapped only to the period corresponding to its first onset. If there are multiple occurrences of one AE, only the first event is summarized.
- n is the number of subjects in the corresponding time period.
- Total presents the number and proportion of subjects experiencing the event regardless of timing of first onset.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) **長期試験**

有害事象の初回発現時期を Day 1～7、Day 8～14、Day 15～21、Day 22～28、Day 29～35、Day 36～42、Day 43 以降で区分、及び Day 1～84、Day 85～168、Day 169～252、Day 253～364、Day 365 以降で区分した主な有害事象の初回発現時期別の発現割合を表 2.7.4.2-10 及び表 2.7.4.2-11 に示す。

長期試験から実薬投与を開始した DB-PLCB で、投与開始後 6 週までにアカシジアを初回発現した被験者は Day 21 までおらず、Day 22～28 に 1 名が発現し、Day 29 以降はいなかった。また、アカシジアを含むいずれの主な有害事象も投与開始後 6 週までの初回発現時期に明確な特徴はみられなかった。

最終評価時まででは、Overall で投与後半年以降に初めて発現する被験者が多かった有害事象はなかった。

表 2.7.4.2-10　投与開始後 6 週までの初回発現時期別主な有害事象（Overall で発現割合 2%以上）の発現割合（長期試験）

Safety Analysis Set
DB-PLCB, N = 36

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 36	Day 8 to 14 n = 36	Day 15 to 21 n = 36	Day 22 to 28 n = 36	Day 29 to 35 n = 34	Day 36 to 42 n = 34	Day 43 or after n = 34	Total n = 36
Blood and lymphatic system disorders	血液およびリンパ系障害								
Iron deficiency anaemia	鉄欠乏性貧血	0	0	0	1 (2.8%)	0	0	0	1 (2.8%)
Endocrine disorders	内分泌障害								
Hyperprolactinaemia	高プロラクチン血症	0	0	0	0	2 (5.9%)	0	2 (5.9%)	4 (11.1%)
Eye disorders	眼障害								
Conjunctivitis allergic	アレルギー性結膜炎	0	0	2 (5.6%)	0	0	0	2 (5.9%)	4 (11.1%)
Gastrointestinal disorders	胃腸障害								
Vomiting	嘔吐	0	0	0	0	0	0	5 (14.7%)	5 (13.9%)
Constipation	便秘	0	0	0	0	0	0	4 (11.8%)	4 (11.1%)
Diarrhoea	下痢	0	0	0	0	0	0	3 (8.8%)	3 (8.3%)
Abdominal pain	腹痛	0	0	0	1 (2.8%)	1 (2.9%)	1 (2.9%)	2 (5.9%)	5 (13.9%)
Nausea	悪心	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Dental caries	齲歯	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Abdominal discomfort	腹部不快感	0	0	0	0	0	0	3 (8.8%)	3 (8.3%)
Stomatitis	口内炎	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Anal fissure	裂肛	0	0	0	0	0	0	1 (2.9%)	1 (2.8%)
Abdominal pain upper	上腹部痛	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態								
Peripheral swelling	末梢腫脹	0	1 (2.8%)	0	0	0	0	0	1 (2.8%)
Pyrexia	発熱	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Malaise	倦怠感	1 (2.8%)	0	1 (2.8%)	0	1 (2.9%)	0	0	3 (8.3%)

DB-PLCB, N = 36

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 36	Day 8 to 14 n = 36	Day 15 to 21 n = 36	Day 22 to 28 n = 36	Day 29 to 35 n = 34	Day 36 to 42 n = 34	Day 43 or after n = 34	Total n = 36
Infections and infestations	感染症および寄生虫症								
Nasopharyngitis	上咽頭炎	1 (2.8%)	0	1 (2.8%)	0	0	1 (2.9%)	14 (41.2%)	17 (47.2%)
Bronchitis	気管支炎	1 (2.8%)	0	0	0	0	0	1 (2.9%)	2 (5.6%)
Hordeolum	麦粒腫	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Influenza	インフルエンザ	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Conjunctivitis	結膜炎	0	0	0	0	0	0	1 (2.9%)	1 (2.8%)
Otitis media	中耳炎	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症								
Skin abrasion	皮膚擦過傷	0	0	0	0	1 (2.9%)	0	4 (11.8%)	5 (13.9%)
Wound	創傷	0	0	1 (2.8%)	0	0	0	2 (5.9%)	3 (8.3%)
Arthropod sting	節足動物刺傷	0	0	0	2 (5.6%)	0	0	0	2 (5.6%)
Contusion	挫傷	0	0	0	0	0	0	1 (2.9%)	1 (2.8%)
Ligament sprain	靭帯捻挫	0	0	0	0	1 (2.9%)	0	1 (2.9%)	2 (5.6%)
Investigations	臨床検査								
Weight increased	体重増加	0	0	0	0	0	0	4 (11.8%)	4 (11.1%)
Blood prolactin increased	血中プロラクチン増加	0	0	0	1 (2.8%)	0	0	3 (8.8%)	4 (11.1%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害								
Back pain	背部痛	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Myalgia	筋肉痛	0	0	0	1 (2.8%)	0	0	2 (5.9%)	3 (8.3%)
Pain in extremity	四肢痛	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Arthralgia	関節痛	0	1 (2.8%)	0	0	0	0	1 (2.9%)	2 (5.6%)

DB-PLCB, N = 36

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 36	Day 8 to 14 n = 36	Day 15 to 21 n = 36	Day 22 to 28 n = 36	Day 29 to 35 n = 34	Day 36 to 42 n = 34	Day 43 or after n = 34	Total n = 36
Nervous system disorders	神経系障害								
Akathisia	アカシジア	0	0	0	1 (2.8%)	0	0	5 (14.7%)	6 (16.7%)
Headache	頭痛	0	0	0	0	0	1 (2.9%)	5 (14.7%)	6 (16.7%)
Tremor	振戦	1 (2.8%)	0	0	1 (2.8%)	1 (2.9%)	0	6 (17.6%)	9 (25.0%)
Dystonia	ジストニア	0	1 (2.8%)	0	0	0	0	4 (11.8%)	5 (13.9%)
Somnolence	傾眠	1 (2.8%)	0	0	0	0	0	3 (8.8%)	4 (11.1%)
Dyskinesia	ジスキネジア	0	0	1 (2.8%)	0	0	0	1 (2.9%)	2 (5.6%)
Bradykinesia	運動緩慢	0	0	0	0	0	0	3 (8.8%)	3 (8.3%)
Dizziness	浮動性めまい	0	1 (2.8%)	0	0	0	0	2 (5.9%)	3 (8.3%)
Psychiatric disorders	精神障害								
Schizophrenia	統合失調症	0	0	1 (2.8%)	0	1 (2.9%)	0	8 (23.5%)	10 (27.8%)
Insomnia	不眠症	0	0	0	0	1 (2.9%)	0	1 (2.9%)	2 (5.6%)
Reproductive system and breast disorders	生殖系および乳房障害								
Dysmenorrhoea	月経困難症	0	1 (2.8%)	0	0	0	0	3 (8.8%)	4 (11.1%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害								
Oropharyngeal pain	口腔咽頭痛	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Epistaxis	鼻出血	1 (2.8%)	0	0	0	0	0	0	1 (2.8%)
Rhinitis allergic	アレルギー性鼻炎	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Rhinorrhoea	鼻漏	0	0	1 (2.8%)	0	0	0	0	1 (2.8%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害								
Acne	ざ瘡	0	1 (2.8%)	0	0	1 (2.9%)	0	6 (17.6%)	8 (22.2%)

DB-PLCB, N = 36

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 36	Day 8 to 14 n = 36	Day 15 to 21 n = 36	Day 22 to 28 n = 36	Day 29 to 35 n = 34	Day 36 to 42 n = 34	Day 43 or after n = 34	Total n = 36
Eczema	湿疹	0	0	0	0	0	0	7 (20.6%)	7 (19.4%)
Pruritus	そう痒症	0	0	0	0	0	0	2 (5.9%)	2 (5.6%)
Dermatitis contact	接触皮膚炎	0	0	0	0	0	0	1 (2.9%)	1 (2.8%)
Erythema	紅斑	0	0	0	0	0	0	1 (2.9%)	1 (2.8%)
Haemorrhage subcutaneous	皮下出血	0	0	0	0	0	0	1 (2.9%)	1 (2.8%)
Ingrowing nail	嵌入爪	0	0	0	0	0	0	1 (2.9%)	1 (2.8%)
Rash	発疹	0	0	1 (2.8%)	0	0	0	1 (2.9%)	2 (5.6%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 37	Day 8 to 14 n = 36	Day 15 to 21 n = 35	Day 22 to 28 n = 35	Day 29 to 35 n = 35	Day 36 to 42 n = 35	Day 43 or after n = 35	Total n = 37
Blood and lymphatic system disorders	血液およびリンパ系障害								
Iron deficiency anaemia	鉄欠乏性貧血	0	0	0	0	0	0	2 (5.7%)	2 (5.4%)
Endocrine disorders	内分泌障害								
Hyperprolactinaemia	高プロラクチン血症	0	0	0	0	0	0	4 (11.4%)	4 (10.8%)
Eye disorders	眼障害								
Conjunctivitis allergic	アレルギー性結膜炎	2 (5.4%)	0	0	0	0	0	1 (2.9%)	3 (8.1%)
Gastrointestinal disorders	胃腸障害								
Vomiting	嘔吐	0	1 (2.8%)	0	0	0	0	4 (11.4%)	5 (13.5%)
Constipation	便秘	0	0	0	0	0	0	2 (5.7%)	2 (5.4%)
Diarrhoea	下痢	0	0	0	0	0	0	4 (11.4%)	4 (10.8%)
Abdominal pain	腹痛	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Nausea	悪心	0	0	0	0	0	0	3 (8.6%)	3 (8.1%)
Dental caries	齲歯	0	0	0	0	0	1 (2.9%)	2 (5.7%)	3 (8.1%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 37	Day 8 to 14 n = 36	Day 15 to 21 n = 35	Day 22 to 28 n = 35	Day 29 to 35 n = 35	Day 36 to 42 n = 35	Day 43 or after n = 35	Total n = 37
Abdominal discomfort	腹部不快感	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Anal fissure	裂肛	0	0	0	0	1 (2.9%)	0	2 (5.7%)	3 (8.1%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態								
Peripheral swelling	末梢腫脹	0	0	1 (2.9%)	0	0	0	1 (2.9%)	2 (5.4%)
Pyrexia	発熱	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Immune system disorders	免疫系障害								
Seasonal allergy	季節性アレルギー	0	0	0	0	0	0	2 (5.7%)	2 (5.4%)
Infections and infestations	感染症および寄生虫症								
Nasopharyngitis	上咽頭炎	1 (2.7%)	2 (5.6%)	1 (2.9%)	0	1 (2.9%)	0	8 (22.9%)	13 (35.1%)
Bronchitis	気管支炎	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Influenza	インフルエンザ	0	0	0	0	0	0	3 (8.6%)	3 (8.1%)
Pharyngitis	咽頭炎	0	1 (2.8%)	0	0	0	0	1 (2.9%)	2 (5.4%)
Conjunctivitis	結膜炎	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Gastroenteritis	胃腸炎	0	0	0	0	0	0	2 (5.7%)	2 (5.4%)
Otitis media	中耳炎	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症								
Skin abrasion	皮膚擦過傷	1 (2.7%)	0	0	0	0	1 (2.9%)	1 (2.9%)	3 (8.1%)
Arthropod sting	節足動物刺傷	1 (2.7%)	1 (2.8%)	1 (2.9%)	0	0	1 (2.9%)	1 (2.9%)	5 (13.5%)
Contusion	挫傷	0	0	0	0	0	0	3 (8.6%)	3 (8.1%)
Ligament sprain	靭帯捻挫	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Investigations	臨床検査								
Weight increased	体重増加	0	0	1 (2.9%)	0	1 (2.9%)	0	5 (14.3%)	7 (18.9%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 37	Day 8 to 14 n = 36	Day 15 to 21 n = 35	Day 22 to 28 n = 35	Day 29 to 35 n = 35	Day 36 to 42 n = 35	Day 43 or after n = 35	Total n = 37
Blood prolactin increased	血中プロラクチン増加	0	0	0	0	0	0	4 (11.4%)	4 (10.8%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	0	0	0	1 (2.9%)	0	0	2 (5.7%)	3 (8.1%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害								
Back pain	背部痛	0	0	1 (2.9%)	0	0	0	2 (5.7%)	3 (8.1%)
Myalgia	筋肉痛	0	0	0	0	0	0	5 (14.3%)	5 (13.5%)
Pain in extremity	四肢痛	0	0	0	0	0	0	2 (5.7%)	2 (5.4%)
Arthralgia	関節痛	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Nervous system disorders	神経系障害								
Akathisia	アカシジア	1 (2.7%)	2 (5.6%)	2 (5.7%)	0	1 (2.9%)	0	4 (11.4%)	10 (27.0%)
Headache	頭痛	0	1 (2.8%)	1 (2.9%)	0	0	0	5 (14.3%)	7 (18.9%)
Tremor	振戦	0	1 (2.8%)	0	0	0	0	4 (11.4%)	5 (13.5%)
Dystonia	ジストニア	0	0	0	0	0	0	4 (11.4%)	4 (10.8%)
Somnolence	傾眠	1 (2.7%)	0	0	0	1 (2.9%)	0	2 (5.7%)	4 (10.8%)
Dyskinesia	ジスキネジア	0	0	0	0	0	0	2 (5.7%)	2 (5.4%)
Psychiatric disorders	精神障害								
Schizophrenia	統合失調症	0	0	0	1 (2.9%)	0	0	4 (11.4%)	5 (13.5%)
Insomnia	不眠症	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Intentional self-injury	故意の自傷行為	0	0	0	0	0	0	2 (5.7%)	2 (5.4%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害								
Oropharyngeal pain	口腔咽頭痛	0	1 (2.8%)	0	0	0	0	2 (5.7%)	3 (8.1%)
Epistaxis	鼻出血	1 (2.7%)	1 (2.8%)	0	0	0	1 (2.9%)	0	3 (8.1%)
Rhinitis allergic	アレルギー性鼻炎	0	0	0	0	0	1 (2.9%)	0	1 (2.7%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 37	Day 8 to 14 n = 36	Day 15 to 21 n = 35	Day 22 to 28 n = 35	Day 29 to 35 n = 35	Day 36 to 42 n = 35	Day 43 or after n = 35	Total n = 37
Rhinorrhoea	鼻漏	0	0	0	1 (2.9%)	0	0	0	1 (2.7%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害								
Acne	ざ瘡	0	1 (2.8%)	1 (2.9%)	0	0	1 (2.9%)	2 (5.7%)	5 (13.5%)
Eczema	湿疹	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Pruritus	そう痒症	0	0	0	1 (2.9%)	0	1 (2.9%)	2 (5.7%)	4 (10.8%)
Dermatitis contact	接触皮膚炎	0	0	0	0	0	0	1 (2.9%)	1 (2.7%)
Haemorrhage subcutaneous	皮下出血	0	1 (2.8%)	0	0	0	0	0	1 (2.7%)
Ingrowing nail	嵌入爪	0	0	0	0	0	0	2 (5.7%)	2 (5.4%)
Rash	発疹	0	0	0	0	1 (2.9%)	0	0	1 (2.7%)

DB-16MG, N = 33

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 33	Day 8 to 14 n = 33	Day 15 to 21 n = 32	Day 22 to 28 n = 32	Day 29 to 35 n = 32	Day 36 to 42 n = 31	Day 43 or after n = 31	Total n = 33
Endocrine disorders	内分泌障害								
Hyperprolactinaemia	高プロラクチン血症	0	0	0	0	0	0	2 (6.5%)	2 (6.1%)
Eye disorders	眼障害								
Conjunctivitis allergic	アレルギー性結膜炎	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Gastrointestinal disorders	胃腸障害								
Vomiting	嘔吐	0	2 (6.1%)	0	0	0	0	3 (9.7%)	5 (15.2%)
Constipation	便秘	0	0	0	0	0	0	5 (16.1%)	5 (15.2%)
Diarrhoea	下痢	0	0	0	0	0	0	3 (9.7%)	3 (9.1%)
Abdominal pain	腹痛	1 (3.0%)	0	1 (3.1%)	0	0	0	1 (3.2%)	3 (9.1%)
Nausea	悪心	0	1 (3.0%)	1 (3.1%)	0	0	0	2 (6.5%)	4 (12.1%)

DB-16MG, N = 33

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 33	Day 8 to 14 n = 33	Day 15 to 21 n = 32	Day 22 to 28 n = 32	Day 29 to 35 n = 32	Day 36 to 42 n = 31	Day 43 or after n = 31	Total n = 33
Dental caries	齲歯	1 (3.0%)	0	0	0	0	0	1 (3.2%)	2 (6.1%)
Abdominal discomfort	腹部不快感	0	0	0	0	0	0	2 (6.5%)	2 (6.1%)
Stomatitis	口内炎	0	1 (3.0%)	0	0	0	0	2 (6.5%)	3 (9.1%)
Toothache	歯痛	0	2 (6.1%)	0	0	0	0	2 (6.5%)	4 (12.1%)
Abdominal pain upper	上腹部痛	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態								
Peripheral swelling	末梢腫脹	0	1 (3.0%)	0	0	0	0	1 (3.2%)	2 (6.1%)
Pyrexia	発熱	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Immune system disorders	免疫系障害								
Seasonal allergy	季節性アレルギー	0	0	0	0	0	0	2 (6.5%)	2 (6.1%)
Infections and infestations	感染症および寄生虫症								
Nasopharyngitis	上咽頭炎	0	0	1 (3.1%)	1 (3.1%)	0	0	6 (19.4%)	8 (24.2%)
Bronchitis	気管支炎	0	0	0	0	0	0	2 (6.5%)	2 (6.1%)
Hordeolum	麦粒腫	0	0	0	0	1 (3.1%)	0	2 (6.5%)	3 (9.1%)
Pharyngitis	咽頭炎	1 (3.0%)	0	0	0	0	0	1 (3.2%)	2 (6.1%)
Conjunctivitis	結膜炎	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Gastroenteritis	胃腸炎	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症								
Skin abrasion	皮膚擦過傷	0	1 (3.0%)	0	1 (3.1%)	0	0	1 (3.2%)	3 (9.1%)
Wound	創傷	1 (3.0%)	0	1 (3.1%)	2 (6.3%)	0	0	1 (3.2%)	5 (15.2%)
Contusion	挫傷	1 (3.0%)	0	0	0	0	0	1 (3.2%)	2 (6.1%)
Ligament sprain	靭帯捻挫	0	1 (3.0%)	0	1 (3.1%)	0	0	0	2 (6.1%)

DB-16MG, N = 33

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 33	Day 8 to 14 n = 33	Day 15 to 21 n = 32	Day 22 to 28 n = 32	Day 29 to 35 n = 32	Day 36 to 42 n = 31	Day 43 or after n = 31	Total n = 33
Investigations	臨床検査								
Weight increased	体重増加	0	0	1 (3.1%)	0	1 (3.1%)	0	2 (6.5%)	4 (12.1%)
Blood prolactin increased	血中プロラクチン増加	0	0	0	0	0	0	2 (6.5%)	2 (6.1%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害								
Back pain	背部痛	1 (3.0%)	0	0	1 (3.1%)	0	0	1 (3.2%)	3 (9.1%)
Pain in extremity	四肢痛	1 (3.0%)	0	0	0	0	0	1 (3.2%)	2 (6.1%)
Arthralgia	関節痛	0	0	0	0	0	0	2 (6.5%)	2 (6.1%)
Nervous system disorders	神経系障害								
Akathisia	アカシジア	2 (6.1%)	0	0	0	0	0	1 (3.2%)	3 (9.1%)
Headache	頭痛	0	2 (6.1%)	1 (3.1%)	1 (3.1%)	0	0	1 (3.2%)	5 (15.2%)
Tremor	振戦	0	0	0	0	0	0	4 (12.9%)	4 (12.1%)
Dystonia	ジストニア	0	0	0	0	0	0	3 (9.7%)	3 (9.1%)
Somnolence	傾眠	0	0	2 (6.3%)	0	0	0	0	2 (6.1%)
Dyskinesia	ジスキネジア	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Bradykinesia	運動緩慢	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Dizziness	浮動性めまい	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Psychiatric disorders	精神障害								
Schizophrenia	統合失調症	0	1 (3.0%)	0	0	0	0	5 (16.1%)	6 (18.2%)
Intentional self-injury	故意の自傷行為	0	1 (3.0%)	0	0	0	0	0	1 (3.0%)
Reproductive system and breast disorders	生殖系および乳房障害								
Dysmenorrhoea	月経困難症	0	1 (3.0%)	0	0	0	0	0	1 (3.0%)

DB-16MG, N = 33

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 33	Day 8 to 14 n = 33	Day 15 to 21 n = 32	Day 22 to 28 n = 32	Day 29 to 35 n = 32	Day 36 to 42 n = 31	Day 43 or after n = 31	Total n = 33
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害								
Oropharyngeal pain	口腔咽頭痛	1 (3.0%)	0	0	0	0	0	3 (9.7%)	4 (12.1%)
Epistaxis	鼻出血	1 (3.0%)	0	0	0	0	0	1 (3.2%)	2 (6.1%)
Rhinitis allergic	アレルギー性鼻炎	0	0	0	0	0	0	2 (6.5%)	2 (6.1%)
Rhinorrhoea	鼻漏	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害								
Acne	ざ瘡	1 (3.0%)	0	0	0	0	0	1 (3.2%)	2 (6.1%)
Eczema	湿疹	0	0	0	0	0	0	2 (6.5%)	2 (6.1%)
Pruritus	そう痒症	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)
Dermatitis contact	接触皮膚炎	0	0	0	0	1 (3.1%)	0	0	1 (3.0%)
Erythema	紅斑	0	0	0	0	0	1 (3.2%)	1 (3.2%)	2 (6.1%)
Haemorrhage subcutaneous	皮下出血	0	0	0	0	0	0	1 (3.2%)	1 (3.0%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 106	Day 8 to 14 n = 105	Day 15 to 21 n = 103	Day 22 to 28 n = 103	Day 29 to 35 n = 101	Day 36 to 42 n = 100	Day 43 or after n = 100	Total n = 106
Blood and lymphatic system disorders	血液およびリンパ系障害								
Iron deficiency anaemia	鉄欠乏性貧血	0	0	0	1 (1.0%)	0	0	2 (2.0%)	3 (2.8%)
Endocrine disorders	内分泌障害								
Hyperprolactinaemia	高プロラクチン血症	0	0	0	0	2 (2.0%)	0	8 (8.0%)	10 (9.4%)
Eye disorders	眼障害								

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 106	Day 8 to 14 n = 105	Day 15 to 21 n = 103	Day 22 to 28 n = 103	Day 29 to 35 n = 101	Day 36 to 42 n = 100	Day 43 or after n = 100	Total n = 106
Conjunctivitis allergic	アレルギー性結膜炎	2 (1.9%)	0	2 (1.9%)	0	0	0	4 (4.0%)	8 (7.5%)
Gastrointestinal disorders	胃腸障害								
Vomiting	嘔吐	0	3 (2.9%)	0	0	0	0	12 (12.0%)	15 (14.2%)
Constipation	便秘	0	0	0	0	0	0	11 (11.0%)	11 (10.4%)
Diarrhoea	下痢	0	0	0	0	0	0	10 (10.0%)	10 (9.4%)
Abdominal pain	腹痛	1 (0.9%)	0	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	4 (4.0%)	9 (8.5%)
Nausea	悪心	0	1 (1.0%)	1 (1.0%)	0	0	0	7 (7.0%)	9 (8.5%)
Dental caries	齲歯	1 (0.9%)	0	0	0	0	1 (1.0%)	5 (5.0%)	7 (6.6%)
Abdominal discomfort	腹部不快感	0	0	0	0	0	0	6 (6.0%)	6 (5.7%)
Stomatitis	口内炎	0	1 (1.0%)	0	0	0	0	4 (4.0%)	5 (4.7%)
Anal fissure	裂肛	0	0	0	0	1 (1.0%)	0	3 (3.0%)	4 (3.8%)
Toothache	歯痛	0	2 (1.9%)	0	0	0	0	2 (2.0%)	4 (3.8%)
Abdominal pain upper	上腹部痛	0	0	0	0	0	0	3 (3.0%)	3 (2.8%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態								
Peripheral swelling	末梢腫脹	0	2 (1.9%)	1 (1.0%)	0	0	0	2 (2.0%)	5 (4.7%)
Pyrexia	発熱	0	0	0	0	0	0	4 (4.0%)	4 (3.8%)
Malaise	倦怠感	1 (0.9%)	0	1 (1.0%)	0	1 (1.0%)	0	0	3 (2.8%)
Immune system disorders	免疫系障害								
Seasonal allergy	季節性アレルギー	0	0	0	0	0	0	4 (4.0%)	4 (3.8%)
Infections and infestations	感染症および寄生虫症								
Nasopharyngitis	上咽頭炎	2 (1.9%)	2 (1.9%)	3 (2.9%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	28 (28.0%)	38 (35.8%)
Bronchitis	気管支炎	1 (0.9%)	0	0	0	0	0	4 (4.0%)	5 (4.7%)
Hordeolum	麦粒腫	0	0	0	0	1 (1.0%)	0	4 (4.0%)	5 (4.7%)
Influenza	インフルエンザ	0	0	0	0	0	0	5 (5.0%)	5 (4.7%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 106	Day 8 to 14 n = 105	Day 15 to 21 n = 103	Day 22 to 28 n = 103	Day 29 to 35 n = 101	Day 36 to 42 n = 100	Day 43 or after n = 100	Total n = 106
Pharyngitis	咽頭炎	1 (0.9%)	1 (1.0%)	0	0	0	0	2 (2.0%)	4 (3.8%)
Conjunctivitis	結膜炎	0	0	0	0	0	0	3 (3.0%)	3 (2.8%)
Gastroenteritis	胃腸炎	0	0	0	0	0	0	3 (3.0%)	3 (2.8%)
Otitis media	中耳炎	0	0	0	0	0	0	3 (3.0%)	3 (2.8%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症								
Skin abrasion	皮膚擦過傷	1 (0.9%)	1 (1.0%)	0	1 (1.0%)	1 (1.0%)	1 (1.0%)	6 (6.0%)	11 (10.4%)
Wound	創傷	1 (0.9%)	0	2 (1.9%)	2 (1.9%)	0	0	3 (3.0%)	8 (7.5%)
Arthropod sting	節足動物刺傷	1 (0.9%)	1 (1.0%)	1 (1.0%)	2 (1.9%)	0	1 (1.0%)	1 (1.0%)	7 (6.6%)
Contusion	挫傷	1 (0.9%)	0	0	0	0	0	5 (5.0%)	6 (5.7%)
Ligament sprain	靭帯捻挫	0	1 (1.0%)	0	1 (1.0%)	1 (1.0%)	0	2 (2.0%)	5 (4.7%)
Investigations	臨床検査								
Weight increased	体重増加	0	0	2 (1.9%)	0	2 (2.0%)	0	11 (11.0%)	15 (14.2%)
Blood prolactin increased	血中プロラクチン増加	0	0	0	1 (1.0%)	0	0	9 (9.0%)	10 (9.4%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	0	0	0	1 (1.0%)	0	0	5 (5.0%)	6 (5.7%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害								
Back pain	背部痛	1 (0.9%)	0	1 (1.0%)	1 (1.0%)	0	0	5 (5.0%)	8 (7.5%)
Myalgia	筋肉痛	0	0	0	1 (1.0%)	0	0	7 (7.0%)	8 (7.5%)
Pain in extremity	四肢痛	1 (0.9%)	0	0	0	0	0	5 (5.0%)	6 (5.7%)
Arthralgia	関節痛	0	1 (1.0%)	0	0	0	0	4 (4.0%)	5 (4.7%)
Nervous system disorders	神経系障害								
Akathisia	アカシジア	3 (2.8%)	2 (1.9%)	2 (1.9%)	1 (1.0%)	1 (1.0%)	0	10 (10.0%)	19 (17.9%)
Headache	頭痛	0	3 (2.9%)	2 (1.9%)	1 (1.0%)	0	1 (1.0%)	11 (11.0%)	18 (17.0%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 106	Day 8 to 14 n = 105	Day 15 to 21 n = 103	Day 22 to 28 n = 103	Day 29 to 35 n = 101	Day 36 to 42 n = 100	Day 43 or after n = 100	Total n = 106
Tremor	振戦	1 (0.9%)	1 (1.0%)	0	1 (1.0%)	1 (1.0%)	0	14 (14.0%)	18 (17.0%)
Dystonia	ジストニア	0	1 (1.0%)	0	0	0	0	11 (11.0%)	12 (11.3%)
Somnolence	傾眠	2 (1.9%)	0	2 (1.9%)	0	1 (1.0%)	0	5 (5.0%)	10 (9.4%)
Dyskinesia	ジスキネジア	0	0	1 (1.0%)	0	0	0	4 (4.0%)	5 (4.7%)
Bradykinesia	運動緩慢	0	0	0	0	0	0	4 (4.0%)	4 (3.8%)
Dizziness	浮動性めまい	0	1 (1.0%)	0	0	0	0	3 (3.0%)	4 (3.8%)
Psychiatric disorders	精神障害								
Schizophrenia	統合失調症	0	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0	17 (17.0%)	21 (19.8%)
Insomnia	不眠症	0	0	0	0	1 (1.0%)	0	2 (2.0%)	3 (2.8%)
Intentional self-injury	故意の自傷行為	0	1 (1.0%)	0	0	0	0	2 (2.0%)	3 (2.8%)
Reproductive system and breast disorders	生殖系および乳房障害								
Dysmenorrhoea	月経困難症	0	2 (1.9%)	0	0	0	0	3 (3.0%)	5 (4.7%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害								
Oropharyngeal pain	口腔咽頭痛	1 (0.9%)	1 (1.0%)	0	0	0	0	7 (7.0%)	9 (8.5%)
Epistaxis	鼻出血	3 (2.8%)	1 (1.0%)	0	0	0	1 (1.0%)	1 (1.0%)	6 (5.7%)
Rhinitis allergic	アレルギー性鼻炎	0	0	0	0	0	1 (1.0%)	4 (4.0%)	5 (4.7%)
Rhinorrhoea	鼻漏	0	0	1 (1.0%)	1 (1.0%)	0	0	1 (1.0%)	3 (2.8%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害								
Acne	ざ瘡	1 (0.9%)	2 (1.9%)	1 (1.0%)	0	1 (1.0%)	1 (1.0%)	9 (9.0%)	15 (14.2%)
Eczema	湿疹	0	0	0	0	0	0	10 (10.0%)	10 (9.4%)
Pruritus	そう痒症	0	0	0	1 (1.0%)	0	1 (1.0%)	5 (5.0%)	7 (6.6%)
Dermatitis contact	接触皮膚炎	0	0	0	0	1 (1.0%)	0	2 (2.0%)	3 (2.8%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 7 n = 106	Day 8 to 14 n = 105	Day 15 to 21 n = 103	Day 22 to 28 n = 103	Day 29 to 35 n = 101	Day 36 to 42 n = 100	Day 43 or after n = 100	Total n = 106
Erythema	紅斑	0	0	0	0	0	1 (1.0%)	2 (2.0%)	3 (2.8%)
Haemorrhage subcutaneous	皮下出血	0	1 (1.0%)	0	0	0	0	2 (2.0%)	3 (2.8%)
Ingrowing nail	嵌入爪	0	0	0	0	0	0	3 (3.0%)	3 (2.8%)
Rash	発疹	0	0	1 (1.0%)	0	1 (1.0%)	0	1 (1.0%)	3 (2.8%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- For each subject, an AE is mapped only to the period corresponding to its first onset. If there are multiple occurrences of one AE, only the first event is summarized.
- n is the number of subjects in the corresponding time period.
- Total presents the number and proportion of subjects experiencing the event regardless of timing of first onset.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-11　最終評価時までの初回発現時期別主な有害事象（Overall で発現割合 2%以上）の発現割合（長期試験）

Safety Analysis Set
DB-PLCB, N = 36

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 36	Day 85 to 168 n = 32	Day 169 to 252 n = 27	Day 253 to 364 n = 23	Day 365 or after n = 16	Total n = 36
Blood and lymphatic system disorders	血液およびリンパ系障害						
Iron deficiency anaemia	鉄欠乏性貧血	1 (2.8%)	0	0	0	0	1 (2.8%)
Endocrine disorders	内分泌障害						
Hyperprolactinaemia	高プロラクチン血症	2 (5.6%)	1 (3.1%)	1 (3.7%)	0	0	4 (11.1%)
Eye disorders	眼障害						
Conjunctivitis allergic	アレルギー性結膜炎	2 (5.6%)	1 (3.1%)	0	1 (4.3%)	0	4 (11.1%)
Gastrointestinal disorders	胃腸障害						
Vomiting	嘔吐	0	1 (3.1%)	2 (7.4%)	1 (4.3%)	1 (6.3%)	5 (13.9%)
Constipation	便秘	1 (2.8%)	2 (6.3%)	0	1 (4.3%)	0	4 (11.1%)
Diarrhoea	下痢	0	0	1 (3.7%)	2 (8.7%)	0	3 (8.3%)
Abdominal pain	腹痛	3 (8.3%)	0	1 (3.7%)	1 (4.3%)	0	5 (13.9%)
Nausea	悪心	1 (2.8%)	0	1 (3.7%)	0	0	2 (5.6%)
Dental caries	齲歯	0	1 (3.1%)	1 (3.7%)	0	0	2 (5.6%)
Abdominal discomfort	腹部不快感	0	1 (3.1%)	0	1 (4.3%)	1 (6.3%)	3 (8.3%)
Stomatitis	口内炎	0	1 (3.1%)	0	1 (4.3%)	0	2 (5.6%)
Anal fissure	裂肛	0	0	0	1 (4.3%)	0	1 (2.8%)
Abdominal pain upper	上腹部痛	0	0	0	1 (4.3%)	1 (6.3%)	2 (5.6%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態						

DB-PLCB, N = 36

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 36	Day 85 to 168 n = 32	Day 169 to 252 n = 27	Day 253 to 364 n = 23	Day 365 or after n = 16	Total n = 36
Peripheral swelling	末梢腫脹	1 (2.8%)	0	0	0	0	1 (2.8%)
Pyrexia	発熱	1 (2.8%)	1 (3.1%)	0	0	0	2 (5.6%)
Malaise	倦怠感	3 (8.3%)	0	0	0	0	3 (8.3%)
Infections and infestations	感染症および寄生虫症						
Nasopharyngitis	上咽頭炎	7 (19.4%)	5 (15.6%)	3 (11.1%)	2 (8.7%)	0	17 (47.2%)
Bronchitis	気管支炎	1 (2.8%)	0	1 (3.7%)	0	0	2 (5.6%)
Hordeolum	麦粒腫	1 (2.8%)	1 (3.1%)	0	0	0	2 (5.6%)
Influenza	インフルエンザ	0	0	2 (7.4%)	0	0	2 (5.6%)
Conjunctivitis	結膜炎	0	1 (3.1%)	0	0	0	1 (2.8%)
Otitis media	中耳炎	1 (2.8%)	1 (3.1%)	0	0	0	2 (5.6%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症						
Skin abrasion	皮膚擦過傷	2 (5.6%)	3 (9.4%)	0	0	0	5 (13.9%)
Wound	創傷	1 (2.8%)	0	1 (3.7%)	1 (4.3%)	0	3 (8.3%)
Arthropod sting	節足動物刺傷	2 (5.6%)	0	0	0	0	2 (5.6%)
Contusion	挫傷	1 (2.8%)	0	0	0	0	1 (2.8%)
Ligament sprain	靭帯捻挫	2 (5.6%)	0	0	0	0	2 (5.6%)
Investigations	臨床検査						
Weight increased	体重増加	0	2 (6.3%)	0	1 (4.3%)	1 (6.3%)	4 (11.1%)
Blood prolactin increased	血中プロラクチン増加	1 (2.8%)	3 (9.4%)	0	0	0	4 (11.1%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	0	1 (3.1%)	0	0	1 (6.3%)	2 (5.6%)

DB-PLCB, N = 36

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 36	Day 85 to 168 n = 32	Day 169 to 252 n = 27	Day 253 to 364 n = 23	Day 365 or after n = 16	Total n = 36
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害						
Back pain	背部痛	1 (2.8%)	0	0	1 (4.3%)	0	2 (5.6%)
Myalgia	筋肉痛	2 (5.6%)	0	1 (3.7%)	0	0	3 (8.3%)
Pain in extremity	四肢痛	0	0	1 (3.7%)	1 (4.3%)	0	2 (5.6%)
Arthralgia	関節痛	1 (2.8%)	0	0	1 (4.3%)	0	2 (5.6%)
Nervous system disorders	神経系障害						
Akathisia	アカシジア	3 (8.3%)	2 (6.3%)	1 (3.7%)	0	0	6 (16.7%)
Headache	頭痛	2 (5.6%)	2 (6.3%)	2 (7.4%)	0	0	6 (16.7%)
Tremor	振戦	5 (13.9%)	2 (6.3%)	1 (3.7%)	1 (4.3%)	0	9 (25.0%)
Dystonia	ジストニア	2 (5.6%)	2 (6.3%)	0	0	1 (6.3%)	5 (13.9%)
Somnolence	傾眠	2 (5.6%)	1 (3.1%)	1 (3.7%)	0	0	4 (11.1%)
Dyskinesia	ジスキネジア	1 (2.8%)	1 (3.1%)	0	0	0	2 (5.6%)
Bradykinesia	運動緩慢	1 (2.8%)	2 (6.3%)	0	0	0	3 (8.3%)
Dizziness	浮動性めまい	2 (5.6%)	0	1 (3.7%)	0	0	3 (8.3%)
Psychiatric disorders	精神障害						
Schizophrenia	統合失調症	4 (11.1%)	6 (18.8%)	0	0	0	10 (27.8%)
Insomnia	不眠症	1 (2.8%)	1 (3.1%)	0	0	0	2 (5.6%)
Reproductive system and breast disorders	生殖系および乳房障害						
Dysmenorrhoea	月経困難症	1 (2.8%)	2 (6.3%)	1 (3.7%)	0	0	4 (11.1%)

DB-PLCB, N = 36

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 36	Day 85 to 168 n = 32	Day 169 to 252 n = 27	Day 253 to 364 n = 23	Day 365 or after n = 16	Total n = 36
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害						
Oropharyngeal pain	口腔咽頭痛	2 (5.6%)	0	0	0	0	2 (5.6%)
Epistaxis	鼻出血	1 (2.8%)	0	0	0	0	1 (2.8%)
Rhinitis allergic	アレルギー性鼻炎	0	1 (3.1%)	0	1 (4.3%)	0	2 (5.6%)
Rhinorrhoea	鼻漏	1 (2.8%)	0	0	0	0	1 (2.8%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害						
Acne	ざ瘡	3 (8.3%)	2 (6.3%)	2 (7.4%)	1 (4.3%)	0	8 (22.2%)
Eczema	湿疹	2 (5.6%)	4 (12.5%)	1 (3.7%)	0	0	7 (19.4%)
Pruritus	そう痒症	0	0	1 (3.7%)	0	1 (6.3%)	2 (5.6%)
Dermatitis contact	接触皮膚炎	0	1 (3.1%)	0	0	0	1 (2.8%)
Erythema	紅斑	0	1 (3.1%)	0	0	0	1 (2.8%)
Haemorrhage subcutaneous	皮下出血	0	0	0	1 (4.3%)	0	1 (2.8%)
Ingrowing nail	嵌入爪	0	1 (3.1%)	0	0	0	1 (2.8%)
Rash	発疹	1 (2.8%)	0	1 (3.7%)	0	0	2 (5.6%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 37	Day 85 to 168 n = 31	Day 169 to 252 n = 28	Day 253 to 364 n = 25	Day 365 or after n = 21	Total n = 37
Blood and lymphatic system disorders	血液およびリンパ系障害						
Iron deficiency anaemia	鉄欠乏性貧血	1 (2.7%)	1 (3.2%)	0	0	0	2 (5.4%)
Endocrine disorders	内分泌障害						
Hyperprolactinaemia	高プロラクチン血症	0	2 (6.5%)	1 (3.6%)	1 (4.0%)	0	4 (10.8%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 37	Day 85 to 168 n = 31	Day 169 to 252 n = 28	Day 253 to 364 n = 25	Day 365 or after n = 21	Total n = 37
Eye disorders	眼障害						
Conjunctivitis allergic	アレルギー性結膜炎	2 (5.4%)	1 (3.2%)	0	0	0	3 (8.1%)
Gastrointestinal disorders	胃腸障害						
Vomiting	嘔吐	2 (5.4%)	3 (9.7%)	0	0	0	5 (13.5%)
Constipation	便秘	1 (2.7%)	0	0	1 (4.0%)	0	2 (5.4%)
Diarrhoea	下痢	1 (2.7%)	2 (6.5%)	0	1 (4.0%)	0	4 (10.8%)
Abdominal pain	腹痛	1 (2.7%)	0	0	0	0	1 (2.7%)
Nausea	悪心	0	1 (3.2%)	1 (3.6%)	1 (4.0%)	0	3 (8.1%)
Dental caries	齲歯	2 (5.4%)	0	0	1 (4.0%)	0	3 (8.1%)
Abdominal discomfort	腹部不快感	1 (2.7%)	0	0	0	0	1 (2.7%)
Anal fissure	裂肛	1 (2.7%)	0	0	1 (4.0%)	1 (4.8%)	3 (8.1%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態						
Peripheral swelling	末梢腫脹	1 (2.7%)	0	0	1 (4.0%)	0	2 (5.4%)
Pyrexia	発熱	0	0	0	1 (4.0%)	0	1 (2.7%)
Immune system disorders	免疫系障害						
Seasonal allergy	季節性アレルギー	0	1 (3.2%)	0	1 (4.0%)	0	2 (5.4%)
Infections and infestations	感染症および寄生虫症						
Nasopharyngitis	上咽頭炎	7 (18.9%)	1 (3.2%)	1 (3.6%)	4 (16.0%)	0	13 (35.1%)
Bronchitis	気管支炎	0	1 (3.2%)	0	0	0	1 (2.7%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 37	Day 85 to 168 n = 31	Day 169 to 252 n = 28	Day 253 to 364 n = 25	Day 365 or after n = 21	Total n = 37
Influenza	インフルエンザ	1 (2.7%)	0	2 (7.1%)	0	0	3 (8.1%)
Pharyngitis	咽頭炎	1 (2.7%)	1 (3.2%)	0	0	0	2 (5.4%)
Conjunctivitis	結膜炎	1 (2.7%)	0	0	0	0	1 (2.7%)
Gastroenteritis	胃腸炎	1 (2.7%)	0	1 (3.6%)	0	0	2 (5.4%)
Otitis media	中耳炎	0	0	0	1 (4.0%)	0	1 (2.7%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症						
Skin abrasion	皮膚擦過傷	2 (5.4%)	0	0	1 (4.0%)	0	3 (8.1%)
Arthropod sting	節足動物刺傷	4 (10.8%)	0	0	1 (4.0%)	0	5 (13.5%)
Contusion	挫傷	1 (2.7%)	0	0	2 (8.0%)	0	3 (8.1%)
Ligament sprain	靭帯捻挫	0	1 (3.2%)	0	0	0	1 (2.7%)
Investigations	臨床検査						
Weight increased	体重増加	5 (13.5%)	0	2 (7.1%)	0	0	7 (18.9%)
Blood prolactin increased	血中プロラクチン増加	1 (2.7%)	1 (3.2%)	1 (3.6%)	1 (4.0%)	0	4 (10.8%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	1 (2.7%)	0	0	2 (8.0%)	0	3 (8.1%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害						
Back pain	背部痛	2 (5.4%)	0	0	1 (4.0%)	0	3 (8.1%)
Myalgia	筋肉痛	0	0	1 (3.6%)	3 (12.0%)	1 (4.8%)	5 (13.5%)
Pain in extremity	四肢痛	0	1 (3.2%)	1 (3.6%)	0	0	2 (5.4%)
Arthralgia	関節痛	0	1 (3.2%)	0	0	0	1 (2.7%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 37	Day 85 to 168 n = 31	Day 169 to 252 n = 28	Day 253 to 364 n = 25	Day 365 or after n = 21	Total n = 37
Nervous system disorders	神経系障害						
Akathisia	アカシジア	7 (18.9%)	1 (3.2%)	2 (7.1%)	0	0	10 (27.0%)
Headache	頭痛	3 (8.1%)	3 (9.7%)	0	1 (4.0%)	0	7 (18.9%)
Tremor	振戦	1 (2.7%)	4 (12.9%)	0	0	0	5 (13.5%)
Dystonia	ジストニア	1 (2.7%)	1 (3.2%)	1 (3.6%)	1 (4.0%)	0	4 (10.8%)
Somnolence	傾眠	2 (5.4%)	1 (3.2%)	1 (3.6%)	0	0	4 (10.8%)
Dyskinesia	ジスキネジア	0	1 (3.2%)	0	1 (4.0%)	0	2 (5.4%)
Psychiatric disorders	精神障害						
Schizophrenia	統合失調症	2 (5.4%)	1 (3.2%)	0	2 (8.0%)	0	5 (13.5%)
Insomnia	不眠症	0	1 (3.2%)	0	0	0	1 (2.7%)
Intentional self-injury	故意の自傷行為	0	0	1 (3.6%)	1 (4.0%)	0	2 (5.4%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害						
Oropharyngeal pain	口腔咽頭痛	1 (2.7%)	1 (3.2%)	0	1 (4.0%)	0	3 (8.1%)
Epistaxis	鼻出血	3 (8.1%)	0	0	0	0	3 (8.1%)
Rhinitis allergic	アレルギー性鼻炎	1 (2.7%)	0	0	0	0	1 (2.7%)
Rhinorrhoea	鼻漏	1 (2.7%)	0	0	0	0	1 (2.7%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害						
Acne	ざ瘡	3 (8.1%)	1 (3.2%)	0	1 (4.0%)	0	5 (13.5%)
Eczema	湿疹	0	0	0	0	1 (4.8%)	1 (2.7%)
Pruritus	そう痒症	2 (5.4%)	0	2 (7.1%)	0	0	4 (10.8%)
Dermatitis contact	接触皮膚炎	0	0	1 (3.6%)	0	0	1 (2.7%)

DB-8MG, N = 37

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 37	Day 85 to 168 n = 31	Day 169 to 252 n = 28	Day 253 to 364 n = 25	Day 365 or after n = 21	Total n = 37
Haemorrhage subcutaneous	皮下出血	1 (2.7%)	0	0	0	0	1 (2.7%)
Ingrowing nail	嵌入爪	0	1 (3.2%)	1 (3.6%)	0	0	2 (5.4%)
Rash	発疹	1 (2.7%)	0	0	0	0	1 (2.7%)

DB-16MG, N = 33

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 33	Day 85 to 168 n = 28	Day 169 to 252 n = 25	Day 253 to 364 n = 20	Day 365 or after n = 9	Total n = 33
Endocrine disorders	内分泌障害						
Hyperprolactinaemia	高プロラクチン血症	0	1 (3.6%)	1 (4.0%)	0	0	2 (6.1%)
Eye disorders	眼障害						
Conjunctivitis allergic	アレルギー性結膜炎	0	0	1 (4.0%)	0	0	1 (3.0%)
Gastrointestinal disorders	胃腸障害						
Vomiting	嘔吐	2 (6.1%)	2 (7.1%)	1 (4.0%)	0	0	5 (15.2%)
Constipation	便秘	1 (3.0%)	2 (7.1%)	2 (8.0%)	0	0	5 (15.2%)
Diarrhoea	下痢	1 (3.0%)	2 (7.1%)	0	0	0	3 (9.1%)
Abdominal pain	腹痛	2 (6.1%)	0	1 (4.0%)	0	0	3 (9.1%)
Nausea	悪心	3 (9.1%)	1 (3.6%)	0	0	0	4 (12.1%)
Dental caries	齲歯	2 (6.1%)	0	0	0	0	2 (6.1%)
Abdominal discomfort	腹部不快感	0	2 (7.1%)	0	0	0	2 (6.1%)
Stomatitis	口内炎	2 (6.1%)	0	1 (4.0%)	0	0	3 (9.1%)
Toothache	歯痛	2 (6.1%)	1 (3.6%)	0	1 (5.0%)	0	4 (12.1%)
Abdominal pain upper	上腹部痛	1 (3.0%)	0	0	0	0	1 (3.0%)

DB-16MG, N = 33

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 33	Day 85 to 168 n = 28	Day 169 to 252 n = 25	Day 253 to 364 n = 20	Day 365 or after n = 9	Total n = 33
General disorders and administration site conditions	一般・全身障害および投与部位の状態						
Peripheral swelling	末梢腫脹	2 (6.1%)	0	0	0	0	2 (6.1%)
Pyrexia	発熱	0	1 (3.6%)	0	0	0	1 (3.0%)
Immune system disorders	免疫系障害						
Seasonal allergy	季節性アレルギー	0	2 (7.1%)	0	0	0	2 (6.1%)
Infections and infestations	感染症および寄生虫症						
Nasopharyngitis	上咽頭炎	4 (12.1%)	0	3 (12.0%)	1 (5.0%)	0	8 (24.2%)
Bronchitis	気管支炎	0	1 (3.6%)	1 (4.0%)	0	0	2 (6.1%)
Hordeolum	麦粒腫	1 (3.0%)	0	0	0	2 (22.2%)	3 (9.1%)
Pharyngitis	咽頭炎	1 (3.0%)	1 (3.6%)	0	0	0	2 (6.1%)
Conjunctivitis	結膜炎	0	1 (3.6%)	0	0	0	1 (3.0%)
Gastroenteritis	胃腸炎	0	1 (3.6%)	0	0	0	1 (3.0%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症						
Skin abrasion	皮膚擦過傷	2 (6.1%)	0	1 (4.0%)	0	0	3 (9.1%)
Wound	創傷	4 (12.1%)	1 (3.6%)	0	0	0	5 (15.2%)
Contusion	挫傷	2 (6.1%)	0	0	0	0	2 (6.1%)
Ligament sprain	靭帯捻挫	2 (6.1%)	0	0	0	0	2 (6.1%)
Investigations	臨床検査						
Weight increased	体重増加	2 (6.1%)	1 (3.6%)	0	1 (5.0%)	0	4 (12.1%)

DB-16MG, N = 33

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 33	Day 85 to 168 n = 28	Day 169 to 252 n = 25	Day 253 to 364 n = 20	Day 365 or after n = 9	Total n = 33
Blood prolactin increased	血中プロラクチン増加	1 (3.0%)	1 (3.6%)	0	0	0	2 (6.1%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	0	1 (3.6%)	0	0	0	1 (3.0%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害						
Back pain	背部痛	2 (6.1%)	1 (3.6%)	0	0	0	3 (9.1%)
Pain in extremity	四肢痛	1 (3.0%)	1 (3.6%)	0	0	0	2 (6.1%)
Arthralgia	関節痛	1 (3.0%)	0	1 (4.0%)	0	0	2 (6.1%)
Nervous system disorders	神経系障害						
Akathisia	アカシジア	3 (9.1%)	0	0	0	0	3 (9.1%)
Headache	頭痛	4 (12.1%)	1 (3.6%)	0	0	0	5 (15.2%)
Tremor	振戦	2 (6.1%)	0	2 (8.0%)	0	0	4 (12.1%)
Dystonia	ジストニア	1 (3.0%)	1 (3.6%)	1 (4.0%)	0	0	3 (9.1%)
Somnolence	傾眠	2 (6.1%)	0	0	0	0	2 (6.1%)
Dyskinesia	ジスキネジア	0	1 (3.6%)	0	0	0	1 (3.0%)
Bradykinesia	運動緩慢	1 (3.0%)	0	0	0	0	1 (3.0%)
Dizziness	浮動性めまい	0	0	0	1 (5.0%)	0	1 (3.0%)
Psychiatric disorders	精神障害						
Schizophrenia	統合失調症	3 (9.1%)	2 (7.1%)	1 (4.0%)	0	0	6 (18.2%)
Intentional self-injury	故意の自傷行為	1 (3.0%)	0	0	0	0	1 (3.0%)
Reproductive system and breast disorders	生殖系および乳房障害						

DB-16MG, N = 33

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 33	Day 85 to 168 n = 28	Day 169 to 252 n = 25	Day 253 to 364 n = 20	Day 365 or after n = 9	Total n = 33
Dysmenorrhoea	月経困難症	1 (3.0%)	0	0	0	0	1 (3.0%)
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害						
Oropharyngeal pain	口腔咽頭痛	2 (6.1%)	1 (3.6%)	0	1 (5.0%)	0	4 (12.1%)
Epistaxis	鼻出血	2 (6.1%)	0	0	0	0	2 (6.1%)
Rhinitis allergic	アレルギー性鼻炎	1 (3.0%)	0	0	1 (5.0%)	0	2 (6.1%)
Rhinorrhoea	鼻漏	0	1 (3.6%)	0	0	0	1 (3.0%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害						
Acne	ざ瘡	1 (3.0%)	0	0	1 (5.0%)	0	2 (6.1%)
Eczema	湿疹	0	1 (3.6%)	1 (4.0%)	0	0	2 (6.1%)
Pruritus	そう痒症	0	1 (3.6%)	0	0	0	1 (3.0%)
Dermatitis contact	接触皮膚炎	1 (3.0%)	0	0	0	0	1 (3.0%)
Erythema	紅斑	2 (6.1%)	0	0	0	0	2 (6.1%)
Haemorrhage subcutaneous	皮下出血	0	0	0	1 (5.0%)	0	1 (3.0%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 106	Day 85 to 168 n = 91	Day 169 to 252 n = 80	Day 253 to 364 n = 68	Day 365 or after n = 46	Total n = 106
Blood and lymphatic system disorders	血液およびリンパ系障害						
Iron deficiency anaemia	鉄欠乏性貧血	2 (1.9%)	1 (1.1%)	0	0	0	3 (2.8%)
Endocrine disorders	内分泌障害						
Hyperprolactinaemia	高プロラクチン血症	2 (1.9%)	4 (4.4%)	3 (3.8%)	1 (1.5%)	0	10 (9.4%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 106	Day 85 to 168 n = 91	Day 169 to 252 n = 80	Day 253 to 364 n = 68	Day 365 or after n = 46	Total n = 106
Eye disorders	眼障害						
Conjunctivitis allergic	アレルギー性結膜炎	4 (3.8%)	2 (2.2%)	1 (1.3%)	1 (1.5%)	0	8 (7.5%)
Gastrointestinal disorders	胃腸障害						
Vomiting	嘔吐	4 (3.8%)	6 (6.6%)	3 (3.8%)	1 (1.5%)	1 (2.2%)	15 (14.2%)
Constipation	便秘	3 (2.8%)	4 (4.4%)	2 (2.5%)	2 (2.9%)	0	11 (10.4%)
Diarrhoea	下痢	2 (1.9%)	4 (4.4%)	1 (1.3%)	3 (4.4%)	0	10 (9.4%)
Abdominal pain	腹痛	6 (5.7%)	0	2 (2.5%)	1 (1.5%)	0	9 (8.5%)
Nausea	悪心	4 (3.8%)	2 (2.2%)	2 (2.5%)	1 (1.5%)	0	9 (8.5%)
Dental caries	齲歯	4 (3.8%)	1 (1.1%)	1 (1.3%)	1 (1.5%)	0	7 (6.6%)
Abdominal discomfort	腹部不快感	1 (0.9%)	3 (3.3%)	0	1 (1.5%)	1 (2.2%)	6 (5.7%)
Stomatitis	口内炎	2 (1.9%)	1 (1.1%)	1 (1.3%)	1 (1.5%)	0	5 (4.7%)
Anal fissure	裂肛	1 (0.9%)	0	0	2 (2.9%)	1 (2.2%)	4 (3.8%)
Toothache	歯痛	2 (1.9%)	1 (1.1%)	0	1 (1.5%)	0	4 (3.8%)
Abdominal pain upper	上腹部痛	1 (0.9%)	0	0	1 (1.5%)	1 (2.2%)	3 (2.8%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態						
Peripheral swelling	末梢腫脹	4 (3.8%)	0	0	1 (1.5%)	0	5 (4.7%)
Pyrexia	発熱	1 (0.9%)	2 (2.2%)	0	1 (1.5%)	0	4 (3.8%)
Malaise	倦怠感	3 (2.8%)	0	0	0	0	3 (2.8%)
Immune system disorders	免疫系障害						
Seasonal allergy	季節性アレルギー	0	3 (3.3%)	0	1 (1.5%)	0	4 (3.8%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 106	Day 85 to 168 n = 91	Day 169 to 252 n = 80	Day 253 to 364 n = 68	Day 365 or after n = 46	Total n = 106
Infections and infestations	感染症および寄生虫症						
Nasopharyngitis	上咽頭炎	18 (17.0%)	6 (6.6%)	7 (8.8%)	7 (10.3%)	0	38 (35.8%)
Bronchitis	気管支炎	1 (0.9%)	2 (2.2%)	2 (2.5%)	0	0	5 (4.7%)
Hordeolum	麦粒腫	2 (1.9%)	1 (1.1%)	0	0	2 (4.3%)	5 (4.7%)
Influenza	インフルエンザ	1 (0.9%)	0	4 (5.0%)	0	0	5 (4.7%)
Pharyngitis	咽頭炎	2 (1.9%)	2 (2.2%)	0	0	0	4 (3.8%)
Conjunctivitis	結膜炎	1 (0.9%)	2 (2.2%)	0	0	0	3 (2.8%)
Gastroenteritis	胃腸炎	1 (0.9%)	1 (1.1%)	1 (1.3%)	0	0	3 (2.8%)
Otitis media	中耳炎	1 (0.9%)	1 (1.1%)	0	1 (1.5%)	0	3 (2.8%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症						
Skin abrasion	皮膚擦過傷	6 (5.7%)	3 (3.3%)	1 (1.3%)	1 (1.5%)	0	11 (10.4%)
Wound	創傷	5 (4.7%)	1 (1.1%)	1 (1.3%)	1 (1.5%)	0	8 (7.5%)
Arthropod sting	節足動物刺傷	6 (5.7%)	0	0	1 (1.5%)	0	7 (6.6%)
Contusion	挫傷	4 (3.8%)	0	0	2 (2.9%)	0	6 (5.7%)
Ligament sprain	靭帯捻挫	4 (3.8%)	1 (1.1%)	0	0	0	5 (4.7%)
Investigations	臨床検査						
Weight increased	体重増加	7 (6.6%)	3 (3.3%)	2 (2.5%)	2 (2.9%)	1 (2.2%)	15 (14.2%)
Blood prolactin increased	血中プロラクチン増加	3 (2.8%)	5 (5.5%)	1 (1.3%)	1 (1.5%)	0	10 (9.4%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	1 (0.9%)	2 (2.2%)	0	2 (2.9%)	1 (2.2%)	6 (5.7%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 106	Day 85 to 168 n = 91	Day 169 to 252 n = 80	Day 253 to 364 n = 68	Day 365 or after n = 46	Total n = 106
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害						
Back pain	背部痛	5 (4.7%)	1 (1.1%)	0	2 (2.9%)	0	8 (7.5%)
Myalgia	筋肉痛	2 (1.9%)	0	2 (2.5%)	3 (4.4%)	1 (2.2%)	8 (7.5%)
Pain in extremity	四肢痛	1 (0.9%)	2 (2.2%)	2 (2.5%)	1 (1.5%)	0	6 (5.7%)
Arthralgia	関節痛	2 (1.9%)	1 (1.1%)	1 (1.3%)	1 (1.5%)	0	5 (4.7%)
Nervous system disorders	神経系障害						
Akathisia	アカシジア	13 (12.3%)	3 (3.3%)	3 (3.8%)	0	0	19 (17.9%)
Headache	頭痛	9 (8.5%)	6 (6.6%)	2 (2.5%)	1 (1.5%)	0	18 (17.0%)
Tremor	振戦	8 (7.5%)	6 (6.6%)	3 (3.8%)	1 (1.5%)	0	18 (17.0%)
Dystonia	ジストニア	4 (3.8%)	4 (4.4%)	2 (2.5%)	1 (1.5%)	1 (2.2%)	12 (11.3%)
Somnolence	傾眠	6 (5.7%)	2 (2.2%)	2 (2.5%)	0	0	10 (9.4%)
Dyskinesia	ジスキネジア	1 (0.9%)	3 (3.3%)	0	1 (1.5%)	0	5 (4.7%)
Bradykinesia	運動緩慢	2 (1.9%)	2 (2.2%)	0	0	0	4 (3.8%)
Dizziness	浮動性めまい	2 (1.9%)	0	1 (1.3%)	1 (1.5%)	0	4 (3.8%)
Psychiatric disorders	精神障害						
Schizophrenia	統合失調症	9 (8.5%)	9 (9.9%)	1 (1.3%)	2 (2.9%)	0	21 (19.8%)
Insomnia	不眠症	1 (0.9%)	2 (2.2%)	0	0	0	3 (2.8%)
Intentional self-injury	故意の自傷行為	1 (0.9%)	0	1 (1.3%)	1 (1.5%)	0	3 (2.8%)
Reproductive system and breast disorders	生殖系および乳房障害						
Dysmenorrhoea	月経困難症	2 (1.9%)	2 (2.2%)	1 (1.3%)	0	0	5 (4.7%)

Overall, N = 106

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	Day 1 to 84 n = 106	Day 85 to 168 n = 91	Day 169 to 252 n = 80	Day 253 to 364 n = 68	Day 365 or after n = 46	Total n = 106
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害						
Oropharyngeal pain	口腔咽頭痛	5 (4.7%)	2 (2.2%)	0	2 (2.9%)	0	9 (8.5%)
Epistaxis	鼻出血	6 (5.7%)	0	0	0	0	6 (5.7%)
Rhinitis allergic	アレルギー性鼻炎	2 (1.9%)	1 (1.1%)	0	2 (2.9%)	0	5 (4.7%)
Rhinorrhoea	鼻漏	2 (1.9%)	1 (1.1%)	0	0	0	3 (2.8%)
Skin and subcutaneous tissue disorders	皮膚および皮下組織障害						
Acne	ざ瘡	7 (6.6%)	3 (3.3%)	2 (2.5%)	3 (4.4%)	0	15 (14.2%)
Eczema	湿疹	2 (1.9%)	5 (5.5%)	2 (2.5%)	0	1 (2.2%)	10 (9.4%)
Pruritus	そう痒症	2 (1.9%)	1 (1.1%)	3 (3.8%)	0	1 (2.2%)	7 (6.6%)
Dermatitis contact	接触皮膚炎	1 (0.9%)	1 (1.1%)	1 (1.3%)	0	0	3 (2.8%)
Erythema	紅斑	2 (1.9%)	1 (1.1%)	0	0	0	3 (2.8%)
Haemorrhage subcutaneous	皮下出血	1 (0.9%)	0	0	2 (2.9%)	0	3 (2.8%)
Ingrowing nail	嵌入爪	0	2 (2.2%)	1 (1.3%)	0	0	3 (2.8%)
Rash	発疹	2 (1.9%)	0	1 (1.3%)	0	0	3 (2.8%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- For each subject, an AE is mapped only to the period corresponding to its first onset. If there are multiple occurrences of one AE, only the first event is summarized.
- n is the number of subjects in the corresponding time period.
- Total presents the number and proportion of subjects experiencing the event regardless of timing of first onset.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.2　死亡

検証試験で死亡した被験者はいなかった。長期試験では2名が死亡した。いずれも自殺既遂で、1[redacted]歳[redacted]性はDay 145に、1[redacted]歳[redacted]性はDay 114（服薬終了6日後）に死亡した。いずれも治験薬との因果関係は否定された。

長期試験の死亡に至った有害事象の発現割合を表 2.7.4.2-12 に、被験者ごとの死亡に至った有害事象の一覧を2.7.4.7項付録に示す。

表 2.7.4.2-12　死亡に至った有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any AE leading to death		0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Psychiatric disorders	精神障害	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Completed suicide	自殺既遂	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)

- Abbreviations: AE, adverse event.
- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.3　その他の重篤な有害事象

(1) 検証試験

検証試験で発現した重篤な有害事象の発現割合を表 2.7.4.2-13、被験者ごとの重篤な有害事象の一覧を2.7.4.7項付録に示す。重篤な有害事象は8 mg/日群の1名に過換気が、プラセボ群の1名に統合失調症が発現した。過換気（中等度）はDay 2に発現し、事象に対する治療後に回復し、治験薬の投与は継続された。治験薬の服薬に対する緊張があったと考えられ、治験薬との因果関係は否定されなかった。統合失調症（重度）はDay 13に発現し、治験薬の投与を中止した。転帰は未回復で因果関係は否定されなかった。

表 2.7.4.2-13　重篤な有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Serious AE		1 (2.1%)	1 (2.0%)	0	1 (1.0%)
Psychiatric disorders	精神障害	1 (2.1%)	0	0	0
Schizophrenia	統合失調症	1 (2.1%)	0	0	0

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Respiratory, thoracic and mediastinal disorders	呼吸器、胸郭および縦隔障害	0	1 (2.0%)	0	1 (1.0%)
Hyperventilation	過換気	0	1 (2.0%)	0	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験で発現した重篤な有害事象の発現割合を表 2.7.4.2-14 に、被験者ごとの重篤な有害事象の一覧を 2.7.4.7 項付録に示す。治験中の死亡を含む重篤な有害事象は 17 名に 18 件発現した。内訳は、統合失調症 10 名（9.4%）、自殺既遂 2 名（1.9%）、レンサ球菌性咽頭炎、各種物質毒性、衝動行為、自殺念慮及び自殺企図が各 1 名（各 0.9%）であった。このうち、統合失調症（1 名）以外は治験薬との因果関係は否定された。統合失調症（重度）は Day 62 に発現して治験薬の投与を中止し、治療後に回復した。本事象は治験薬投与後の症状悪化のため、治験薬との因果関係は否定されなかった。

治験終了後に発現した事象であるため集計には含まれていないが、治験終了 10 日後に 1 名が切迫早産で入院した。転帰は回復、治験薬との因果関係は不明とされた（2.7.4.5.4 項参照）。

表 2.7.4.2-14　重篤な有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Serious AE		8 (22.2%)	5 (13.5%)	4 (12.1%)	9 (12.9%)	17 (16.0%)
Infections and infestations	感染症および寄生虫症	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Pharyngitis streptococcal	レンサ球菌性咽頭炎	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	1 (2.8%)	0	0	0	1 (0.9%)
Toxicity to various agents	各種物質毒性	1 (2.8%)	0	0	0	1 (0.9%)
Psychiatric disorders	精神障害	7 (19.4%)	5 (13.5%)	3 (9.1%)	8 (11.4%)	15 (14.2%)
Schizophrenia	統合失調症	7 (19.4%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	10 (9.4%)
Completed suicide	自殺既遂	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Impulsive behaviour	衝動行為	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Suicidal ideation	自殺念慮	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Suicide attempt	自殺企図	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Abbreviations: AE, adverse event.
- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.4　その他の重要な有害事象

2.7.4.2.1.4.1　投与中止に至った有害事象

(1) 検証試験

検証試験で発現した投与中止に至った有害事象の発現割合を表 2.7.4.2-15 に、被験者ごとの投与中止に至った有害事象の一覧を 2.7.4.7 項付録に示す。治療期に投与中止に至った有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）で 3 名（6.4%）、5 名（9.8%）及び 6 名（11.3%）に発現した。実薬合計で 2 名以上に発現した投与中止に至った有害事象は、統合失調症（2 名、2 名及び 1 名）、傾眠（0 名、1 名及び 2 名）であった。

表 2.7.4.2-15　投与中止に至った有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any AE leading to discontinuation of study drug		3 (6.4%)	5 (9.8%)	6 (11.3%)	11 (10.6%)
Gastrointestinal disorders	胃腸障害	1 (2.1%)	0	1 (1.9%)	1 (1.0%)
Nausea	悪心	1 (2.1%)	0	1 (1.9%)	1 (1.0%)
Vomiting	嘔吐	0	0	1 (1.9%)	1 (1.0%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	0	0	1 (1.9%)	1 (1.0%)
Malaise	倦怠感	0	0	1 (1.9%)	1 (1.0%)
Hepatobiliary disorders	肝胆道系障害	0	1 (2.0%)	0	1 (1.0%)
Hepatic function abnormal	肝機能異常	0	1 (2.0%)	0	1 (1.0%)
Infections and infestations	感染症および寄生虫症	0	1 (2.0%)	0	1 (1.0%)
Gastroenteritis	胃腸炎	0	1 (2.0%)	0	1 (1.0%)
Investigations	臨床検査	0	0	1 (1.9%)	1 (1.0%)
Blood prolactin increased	血中プロラクチン増加	0	0	1 (1.9%)	1 (1.0%)
Nervous system disorders	神経系障害	1 (2.1%)	1 (2.0%)	3 (5.7%)	4 (3.8%)
Akathisia	アカシジア	0	0	1 (1.9%)	1 (1.0%)
Somnolence	傾眠	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Headache	頭痛	1 (2.1%)	0	0	0
Psychiatric disorders	精神障害	2 (4.3%)	2 (3.9%)	1 (1.9%)	3 (2.9%)
Schizophrenia	統合失調症	2 (4.3%)	2 (3.9%)	1 (1.9%)	3 (2.9%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験で発現した投与中止に至った有害事象の発現割合を表 2.7.4.2-16 に、被験者ごとの投与中止に至った有害事象の一覧を 2.7.4.7 項付録に示す。投与中止に至った有害事象は 9 名（8.5%）に発現した。内訳は、統合失調症 5 名、自殺既遂 2 名、各種物質毒性、攻撃性及び自殺企図が各 1 名であった。

表 2.7.4.2-16　投与中止に至った有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any AE leading to discontinuation of study drug		4 (11.1%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	9 (8.5%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	1 (2.8%)	0	0	0	1 (0.9%)
Toxicity to various agents	各種物質毒性	1 (2.8%)	0	0	0	1 (0.9%)
Psychiatric disorders	精神障害	3 (8.3%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	8 (7.5%)
Schizophrenia	統合失調症	3 (8.3%)	2 (5.4%)	0	2 (2.9%)	5 (4.7%)
Completed suicide	自殺既遂	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Aggression	攻撃性	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Suicide attempt	自殺企図	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Abbreviations: AE, adverse event.
- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.4.2　減量に至った有害事象及び増量に至った有害事象

長期試験で発現した減量に至った有害事象の発現割合を表 2.7.4.2-17 に、増量に至った有害事象の発現割合を表 2.7.4.2-18 に、被験者ごとの減量に至った有害事象の一覧及び増量に至った有害事象の一覧を 2.7.4.7 項付録に示す。

減量に至った有害事象は 24 名（22.6%）に発現した。内訳は、傾眠 7 名、振戦 5 名、倦怠感、アカシジア及びジストニア各 3 名、悪心及びジスキネジア各 2 名、眼球回転発作、霧視、異常感、食欲減退、運動緩慢、浮動性めまい及び抑うつ気分各 1 名であった。

増量に至った有害事象は 10 名（9.4%）に発現した。内訳は、統合失調症 9 名、過量投与（ロラゼパム）、故意の自傷行為及び自殺念慮各 1 名であった。

表 2.7.4.2-17　減量に至った有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any AE leading to dose decrease of study drug		12 (33.3%)	7 (18.9%)	5 (15.2%)	12 (17.1%)	24 (22.6%)
Eye disorders	眼障害	2 (5.6%)	0	0	0	2 (1.9%)
Oculogyric crisis	眼球回転発作	1 (2.8%)	0	0	0	1 (0.9%)
Vision blurred	霧視	1 (2.8%)	0	0	0	1 (0.9%)
Gastrointestinal disorders	胃腸障害	0	1 (2.7%)	1 (3.0%)	2 (2.9%)	2 (1.9%)
Nausea	悪心	0	1 (2.7%)	1 (3.0%)	2 (2.9%)	2 (1.9%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	3 (8.3%)	1 (2.7%)	0	1 (1.4%)	4 (3.8%)
Malaise	倦怠感	3 (8.3%)	0	0	0	3 (2.8%)
Feeling abnormal	異常感	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Metabolism and nutrition disorders	代謝および栄養障害	1 (2.8%)	0	0	0	1 (0.9%)
Decreased appetite	食欲減退	1 (2.8%)	0	0	0	1 (0.9%)
Nervous system disorders	神経系障害	9 (25.0%)	6 (16.2%)	4 (12.1%)	10 (14.3%)	19 (17.9%)
Akathisia	アカシジア	0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Tremor	振戦	3 (8.3%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	5 (4.7%)
Dystonia	ジストニア	1 (2.8%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	3 (2.8%)
Somnolence	傾眠	4 (11.1%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	7 (6.6%)
Dyskinesia	ジスキネジア	0	2 (5.4%)	0	2 (2.9%)	2 (1.9%)
Bradykinesia	運動緩慢	1 (2.8%)	0	0	0	1 (0.9%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Dizziness	浮動性めまい	1 (2.8%)	0	0	0	1 (0.9%)
Psychiatric disorders	精神障害	1 (2.8%)	0	0	0	1 (0.9%)
Depressed mood	抑うつ気分	1 (2.8%)	0	0	0	1 (0.9%)

- Abbreviations: AE, adverse event.
- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-18　増量に至った有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any AE leading to dose increase of study drug		1 (2.8%)	4 (10.8%)	5 (15.2%)	9 (12.9%)	10 (9.4%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Overdose	過量投与	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Psychiatric disorders	精神障害	1 (2.8%)	4 (10.8%)	5 (15.2%)	9 (12.9%)	10 (9.4%)
Schizophrenia	統合失調症	1 (2.8%)	3 (8.1%)	5 (15.2%)	8 (11.4%)	9 (8.5%)
Intentional self-injury	故意の自傷行為	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Suicidal ideation	自殺念慮	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Abbreviations: AE, adverse event.
- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5　器官別又は症候群別有害事象の解析

ロナセン経口剤又は統合失調症に対する治療薬で注意を要する有害事象をそれぞれ定義し（2.7.4.1.1.2 項参照）、注目すべき有害事象としてその発現状況を評価した。本項ではそれぞれの有害事象を評価し、関連する臨床検査値は 2.7.4.3 項、バイタルサイン、体重、心電図検査は 2.7.4.4 項に示す。

2.7.4.2.1.5.1　悪性症候群関連

(1) 検証試験

悪性症候群関連有害事象の発現状況を表 2.7.4.2-19 に、悪性症候群関連有害事象に該当する各事象の発現割合を表 2.7.4.2-20 に示す。

悪性症候群関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 6.4%、15.7%及び 32.1%に発現し、プラセボ群と比べて 8 mg/日群及び 16 mg/日群で高かった。実薬合計で発現割合が 5%以上であった有害事象は、振戦（0%、9.8%、9.4%）、ジストニア（0%、2.0%、13.2%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-19　悪性症候群関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Neuroleptic malignant syndrome)	3	(6.4%)	4	8	(15.7%)	15	17	(32.1%)	31	25	(24.0%)	46
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Neuroleptic malignant syndrome) related to study drug	2	(4.3%)	3	8	(15.7%)	14	14	(26.4%)	25	22	(21.2%)	39
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-20　悪性症候群関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Neuroleptic malignant syndrome		3 (6.4%)	8 (15.7%)	17 (32.1%)	25 (24.0%)
Gastrointestinal disorders	胃腸障害	0	0	4 (7.5%)	4 (3.8%)
Salivary hypersecretion	流涎過多	0	0	4 (7.5%)	4 (3.8%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
General disorders and administration site conditions	一般・全身障害および投与部位の状態	1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Pyrexia	発熱	1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Investigations	臨床検査	2 (4.3%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	1 (2.1%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
White blood cell count increased	白血球数増加	1 (2.1%)	0	0	0
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	1 (2.1%)	1 (2.0%)	2 (3.8%)	3 (2.9%)
Myalgia	筋肉痛	1 (2.1%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Muscle rigidity	筋固縮	0	0	1 (1.9%)	1 (1.0%)
Nervous system disorders	神経系障害	0	7 (13.7%)	12 (22.6%)	19 (18.3%)
Tremor	振戦	0	5 (9.8%)	5 (9.4%)	10 (9.6%)
Dystonia	ジストニア	0	1 (2.0%)	7 (13.2%)	8 (7.7%)
Myoclonus	ミオクローヌス	0	1 (2.0%)	0	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) **長期試験**

長期試験の悪性症候群関連有害事象の発現状況を表 2.7.4.2-21 に、悪性症候群関連有害事象に該当する各事象の発現割合を表 2.7.4.2-22 に示す。

悪性症候群関連有害事象は 38.7%に発現した。Overall で発現割合が 5%以上であった有害事象は、振戦（17.0%）、ジストニア（11.3%）、筋肉痛（7.5%）、血中クレアチンホスホキナーゼ増加（5.7%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-21　悪性症候群関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Neuroleptic malignant syndrome)	15	(41.7%)	29	15	(40.5%)	20	11	(33.3%)	12	26	(37.1%)	32	41	(38.7%)	61
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	4	(11.1%)	4	2	(5.4%)	2	2	(6.1%)	2	4	(5.7%)	4	8	(7.5%)	8
Leading to dose increase	0			0			0			0			0		
AE (Neuroleptic malignant syndrome) related to study drug	13	(36.1%)	23	10	(27.0%)	12	8	(24.2%)	8	18	(25.7%)	20	31	(29.2%)	43
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	4	(11.1%)	4	2	(5.4%)	2	2	(6.1%)	2	4	(5.7%)	4	8	(7.5%)	8
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-22　悪性症候群関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Neuroleptic malignant syndrome		15 (41.7%)	15 (40.5%)	11 (33.3%)	26 (37.1%)	41 (38.7%)
Cardiac disorders	心臓障害					
Tachycardia	頻脈	1 (2.8%)	0	1 (3.0%)	1 (1.4%)	2 (1.9%)
Gastrointestinal disorders	胃腸障害					
Salivary hypersecretion	流涎過多	2 (5.6%)	0	0	0	2 (1.9%)
Dysphagia	嚥下障害	1 (2.8%)	0	0	0	1 (0.9%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態					
Pyrexia	発熱	2 (5.6%)	1 (2.7%)	1 (3.0%)	2 (2.9%)	4 (3.8%)
Fatigue	疲労	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Investigations	臨床検査					
Blood creatine phosphokinase increased	血中クレアチンホスホキナーゼ増加	2 (5.6%)	3 (8.1%)	1 (3.0%)	4 (5.7%)	6 (5.7%)
White blood cell count increased	白血球数増加	1 (2.8%)	1 (2.7%)	0	1 (1.4%)	2 (1.9%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害					
Myalgia	筋肉痛	3 (8.3%)	5 (13.5%)	0	5 (7.1%)	8 (7.5%)
Muscle rigidity	筋固縮	1 (2.8%)	0	0	0	1 (0.9%)
Muscular weakness	筋力低下	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Nervous system disorders	神経系障害					

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Tremor	振戦	9 (25.0%)	5 (13.5%)	4 (12.1%)	9 (12.9%)	18 (17.0%)
Dystonia	ジストニア	5 (13.9%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	12 (11.3%)
Myoclonus	ミオクローヌス	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.2　錐体外路症状関連

(1) 検証試験

錐体外路症状関連有害事象の発現状況を表 2.7.4.2-23 に、錐体外路症状関連有害事象に該当する各事象の発現割合を表 2.7.4.2-24 に示す。

錐体外路症状関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 4.3%、25.5%及び 50.9%に発現し、プラセボ群と比べて 8 mg/日群及び 16 mg/日群で高かった。実薬合計で発現割合が 5%以上であった有害事象は、アカシジア（4.3%、13.7%、32.1%）、振戦（0%、9.8%、9.4%）、ジストニア（0%、2.0%、13.2%）であった。重篤な事象及び重度の事象はなかった。投与中止に至った事象はアカシジアが 16 mg/日群の 1 名（1.9%）に発現した。

表 2.7.4.2-23　錐体外路症状関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Extrapyramidal syndrome)	2	(4.3%)	3	13	(25.5%)	25	27	(50.9%)	62	40	(38.5%)	87
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			1	(1.9%)	1	1	(1.0%)	1
AE (Extrapyramidal syndrome) related to study drug	2	(4.3%)	3	13	(25.5%)	25	26	(49.1%)	61	39	(37.5%)	86
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			1	(1.9%)	1	1	(1.0%)	1

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-24　錐体外路症状関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Extrapyramidal syndrome		2 (4.3%)	13 (25.5%)	27 (50.9%)	40 (38.5%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Eye disorders	眼障害	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Oculogyric crisis	眼球回転発作	0	1 (2.0%)	2 (3.8%)	3 (2.9%)
Gastrointestinal disorders	胃腸障害	0	0	4 (7.5%)	4 (3.8%)
Salivary hypersecretion	流涎過多	0	0	4 (7.5%)	4 (3.8%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害	0	0	1 (1.9%)	1 (1.0%)
Muscle rigidity	筋固縮	0	0	1 (1.9%)	1 (1.0%)
Nervous system disorders	神経系障害	2 (4.3%)	12 (23.5%)	25 (47.2%)	37 (35.6%)
Akathisia	アカシジア	2 (4.3%)	7 (13.7%)	17 (32.1%)	24 (23.1%)
Tremor	振戦	0	5 (9.8%)	5 (9.4%)	10 (9.6%)
Dystonia	ジストニア	0	1 (2.0%)	7 (13.2%)	8 (7.7%)
Dyskinesia	ジスキネジア	0	0	3 (5.7%)	3 (2.9%)
Bradykinesia	運動緩慢	0	1 (2.0%)	1 (1.9%)	2 (1.9%)
Extrapyramidal disorder	錐体外路障害	0	1 (2.0%)	0	1 (1.0%)
Myoclonus	ミオクローヌス	0	1 (2.0%)	0	1 (1.0%)
Parkinsonian gait	パーキンソン歩行	0	0	1 (1.9%)	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験の錐体外路症状関連有害事象の発現状況を表 2.7.4.2-25 に、錐体外路症状関連有害事象に該当する各事象の発現割合を表 2.7.4.2-26 に示す。

錐体外路症状関連有害事象は 38.7%に発現した。Overall で発現割合が 5%以上であった有害事象は、アカシジア（17.9%）、振戦（17.0%）、ジストニア（11.3%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-25　錐体外路症状関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Extrapyramidal syndrome)	17	(47.2%)	34	13	(35.1%)	24	11	(33.3%)	16	24	(34.3%)	40	41	(38.7%)	74
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	5	(13.9%)	6	4	(10.8%)	6	3	(9.1%)	3	7	(10.0%)	9	12	(11.3%)	15
Leading to dose increase	0			0			0			0			0		
AE (Extrapyramidal syndrome) related to study drug	17	(47.2%)	34	13	(35.1%)	24	9	(27.3%)	13	22	(31.4%)	37	39	(36.8%)	71
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	5	(13.9%)	6	4	(10.8%)	6	3	(9.1%)	3	7	(10.0%)	9	12	(11.3%)	15
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-26　錐体外路症状関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Extrapyramidal syndrome		17 (47.2%)	13 (35.1%)	11 (33.3%)	24 (34.3%)	41 (38.7%)
Eye disorders	眼障害					
Oculogyric crisis	眼球回転発作	1 (2.8%)	1 (2.7%)	0	1 (1.4%)	2 (1.9%)
Gastrointestinal disorders	胃腸障害					
Salivary hypersecretion	流涎過多	2 (5.6%)	0	0	0	2 (1.9%)
Musculoskeletal and connective tissue disorders	筋骨格系および結合組織障害					
Musculoskeletal stiffness	筋骨格硬直	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Muscle rigidity	筋固縮	1 (2.8%)	0	0	0	1 (0.9%)
Muscle tightness	筋緊張	1 (2.8%)	0	0	0	1 (0.9%)
Nervous system disorders	神経系障害					
Akathisia	アカシジア	6 (16.7%)	10 (27.0%)	3 (9.1%)	13 (18.6%)	19 (17.9%)
Tremor	振戦	9 (25.0%)	5 (13.5%)	4 (12.1%)	9 (12.9%)	18 (17.0%)
Dystonia	ジストニア	5 (13.9%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	12 (11.3%)
Dyskinesia	ジスキネジア	2 (5.6%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	5 (4.7%)
Bradykinesia	運動緩慢	3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Myoclonus	ミオクローヌス	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.3　消化器系

(1) 検証試験

消化器系有害事象の発現状況を表 2.7.4.2-27 に、消化器系有害事象に該当する各事象の発現割合を表 2.7.4.2-28 に示す。

消化器系有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 14.9%、29.4%及び 30.2%に発現し、プラセボ群と比べて 8 mg/日群及び 16 mg/日群で高かった。実薬合計で発現割合が 5%以上であった有害事象は悪心（8.5%、9.8%、7.5%）であった。重篤な事象及び重度の事象はなかった。投与中止に至った事象は悪心がプラセボ群の 1 名（2.1%）及び 16 mg/日群の 1 名（1.9%）に、嘔吐が 16 mg/日群の 1 名（1.9%）に発現した。

表 2.7.4.2-27　消化器系有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Gastrointestinal)	7	(14.9%)	11	15	(29.4%)	24	16	(30.2%)	27	31	(29.8%)	51
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	1	(2.1%)	1	0			1	(1.9%)	2	1	(1.0%)	2
AE (Gastrointestinal) related to study drug	4	(8.5%)	6	4	(7.8%)	5	9	(17.0%)	16	13	(12.5%)	21
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	1	(2.1%)	1	0			1	(1.9%)	2	1	(1.0%)	2

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-28　消化器系有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Gastrointestinal		7 (14.9%)	15 (29.4%)	16 (30.2%)	31 (29.8%)
Gastrointestinal disorders	胃腸障害	7 (14.9%)	15 (29.4%)	16 (30.2%)	31 (29.8%)
Nausea	悪心	4 (8.5%)	5 (9.8%)	4 (7.5%)	9 (8.7%)
Vomiting	嘔吐	2 (4.3%)	1 (2.0%)	4 (7.5%)	5 (4.8%)
Abdominal pain	腹痛	2 (4.3%)	1 (2.0%)	3 (5.7%)	4 (3.8%)
Dental caries	齲歯	0	4 (7.8%)	0	4 (3.8%)
Salivary hypersecretion	流涎過多	0	0	4 (7.5%)	4 (3.8%)
Constipation	便秘	0	0	3 (5.7%)	3 (2.9%)
Gastrointestinal disorder	胃腸障害	0	1 (2.0%)	1 (1.9%)	2 (1.9%)
Toothache	歯痛	0	2 (3.9%)	0	2 (1.9%)
Abdominal pain upper	上腹部痛	0	0	1 (1.9%)	1 (1.0%)
Chapped lips	口唇のひび割れ	0	1 (2.0%)	0	1 (1.0%)
Cheilitis	口唇炎	0	1 (2.0%)	0	1 (1.0%)
Diarrhoea	下痢	0	1 (2.0%)	0	1 (1.0%)
Glossodynia	舌痛	0	1 (2.0%)	0	1 (1.0%)
Lip dry	口唇乾燥	1 (2.1%)	0	1 (1.9%)	1 (1.0%)
Sensitivity of teeth	歯の知覚過敏	0	1 (2.0%)	0	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験の消化器系有害事象の発現状況を表 2.7.4.2-29 に、消化器系有害事象に該当する各事象の発現割合を表 2.7.4.2-30 に示す。

消化器系有害事象は 39.6%に発現した。Overall で発現割合が 5%以上であった有害事象は、嘔吐（14.2%）、便秘（10.4%）、下痢（9.4%）、腹痛（8.5%）、悪心（8.5%）、齲歯（6.6%）、腹部不快感（5.7%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-29　消化器系有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Gastrointestinal)	14	(38.9%)	45	15	(40.5%)	32	13	(39.4%)	38	28	(40.0%)	70	42	(39.6%)	115
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			1	(2.7%)	1	1	(3.0%)	1	2	(2.9%)	2	2	(1.9%)	2
Leading to dose increase	0			0			0			0			0		
AE (Gastrointestinal) related to study drug	6	(16.7%)	9	3	(8.1%)	5	5	(15.2%)	9	8	(11.4%)	14	14	(13.2%)	23
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			1	(3.0%)	1	1	(1.4%)	1	1	(0.9%)	1
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-30　消化器系有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Gastrointestinal		14 (38.9%)	15 (40.5%)	13 (39.4%)	28 (40.0%)	42 (39.6%)
Gastrointestinal disorders	胃腸障害					
Vomiting	嘔吐	5 (13.9%)	5 (13.5%)	5 (15.2%)	10 (14.3%)	15 (14.2%)
Constipation	便秘	4 (11.1%)	2 (5.4%)	5 (15.2%)	7 (10.0%)	11 (10.4%)
Diarrhoea	下痢	3 (8.3%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	10 (9.4%)
Abdominal pain	腹痛	5 (13.9%)	1 (2.7%)	3 (9.1%)	4 (5.7%)	9 (8.5%)
Nausea	悪心	2 (5.6%)	3 (8.1%)	4 (12.1%)	7 (10.0%)	9 (8.5%)
Dental caries	齲歯	2 (5.6%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	7 (6.6%)
Abdominal discomfort	腹部不快感	3 (8.3%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	6 (5.7%)
Stomatitis	口内炎	2 (5.6%)	0	3 (9.1%)	3 (4.3%)	5 (4.7%)
Anal fissure	裂肛	1 (2.8%)	3 (8.1%)	0	3 (4.3%)	4 (3.8%)
Toothache	歯痛	0	0	4 (12.1%)	4 (5.7%)	4 (3.8%)
Abdominal pain upper	上腹部痛	2 (5.6%)	0	1 (3.0%)	1 (1.4%)	3 (2.8%)
Salivary hypersecretion	流涎過多	2 (5.6%)	0	0	0	2 (1.9%)
Abdominal pain lower	下腹部痛	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Aphthous ulcer	アフタ性潰瘍	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Chronic gastritis	慢性胃炎	1 (2.8%)	0	0	0	1 (0.9%)
Dysphagia	嚥下障害	1 (2.8%)	0	0	0	1 (0.9%)
Enterocolitis	腸炎	1 (2.8%)	0	0	0	1 (0.9%)
Gingival bleeding	歯肉出血	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Gingival pain	歯肉痛	1 (2.8%)	0	0	0	1 (0.9%)
Lip dry	口唇乾燥	1 (2.8%)	0	0	0	1 (0.9%)
Salivary gland pain	唾液腺痛	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.4　低ナトリウム血症及び抗利尿ホルモン不適合分泌症候群関連

検証試験及び長期試験で、低ナトリウム血症及び抗利尿ホルモン不適合分泌症候群関連有害事象は発現しなかった。

2.7.4.2.1.5.5　血液障害関連

(1) 検証試験

血液障害関連有害事象の発現状況を表 2.7.4.2-31 に、血液障害関連有害事象に該当する各事象の発現割合を表 2.7.4.2-32 に示す。

血液障害関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 2.1%、2.0%及び 0%に発現し、群間に大きな違いはなかった。実薬群で発現した有害事象は貧血（0%、2.0%、0%）のみであった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-31　血液障害関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Blood disorder)	1	(2.1%)	1	1	(2.0%)	2	0			1	(1.0%)	2
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Blood disorder) related to study drug	1	(2.1%)	1	0			0			0		
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-32　血液障害関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Blood disorder		1 (2.1%)	1 (2.0%)	0	1 (1.0%)
Blood and lymphatic system disorders	血液およびリンパ系障害	0	1 (2.0%)	0	1 (1.0%)
Anaemia	貧血	0	1 (2.0%)	0	1 (1.0%)
Investigations	臨床検査	1 (2.1%)	0	0	0
White blood cell count increased	白血球数増加	1 (2.1%)	0	0	0

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) **長期試験**

長期試験の血液障害関連有害事象の発現状況を表 2.7.4.2-33 に、血液障害関連有害事象に該当する各事象の発現割合を表 2.7.4.2-34 に示す。

血液障害関連有害事象は 5.7%に発現した。内訳は、鉄欠乏性貧血（2.8%）、白血球数増加（1.9%）、貧血（0.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-33　血液障害関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Blood disorder)	2	(5.6%)	2	3	(8.1%)	3	1	(3.0%)	1	4	(5.7%)	4	6	(5.7%)	6
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Blood disorder) related to study drug	0			2	(5.4%)	2	0			2	(2.9%)	2	2	(1.9%)	2
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-34　血液障害関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Blood disorder		2 (5.6%)	3 (8.1%)	1 (3.0%)	4 (5.7%)	6 (5.7%)
Blood and lymphatic system disorders	血液およびリンパ系障害					
Iron deficiency anaemia	鉄欠乏性貧血	1 (2.8%)	2 (5.4%)	0	2 (2.9%)	3 (2.8%)
Anaemia	貧血	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Investigations	臨床検査					
White blood cell count increased	白血球数増加	1 (2.8%)	1 (2.7%)	0	1 (1.4%)	2 (1.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.6　肺塞栓症・深部静脈血栓症関連

検証試験及び長期試験で、肺塞栓症・深部静脈血栓症関連有害事象は、発現しなかった。

2.7.4.2.1.5.7　肝機能障害関連

(1) 検証試験

肝機能障害関連有害事象の発現状況を表 2.7.4.2-35 に、肝機能障害関連有害事象に該当する各事象の発現割合を表 2.7.4.2-36 に示す。

肝機能障害関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 2.1%、2.0%及び 1.9%に発現し、群間に大きな違いはなかった。実薬群で発現した有害事象は肝機能異常（0%、2.0%、1.9%）のみであった。重篤な事象及び重度の事象はなかった。投与中止に至った事象は肝機能異常が 8 mg/日群の 1 名（2.0%）に発現した。

表 2.7.4.2-35　肝機能障害関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Hepatic disorders)	1	(2.1%)	2	1	(2.0%)	1	1	(1.9%)	2	2	(1.9%)	3
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			1	(2.0%)	1	0			1	(1.0%)	1
AE (Hepatic disorders) related to study drug	1	(2.1%)	2	1	(2.0%)	1	0			1	(1.0%)	1
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			1	(2.0%)	1	0			1	(1.0%)	1

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-36　肝機能障害関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Hepatic disorders		1 (2.1%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Hepatobiliary disorders	肝胆道系障害	0	1 (2.0%)	1 (1.9%)	2 (1.9%)
Hepatic function abnormal	肝機能異常	0	1 (2.0%)	1 (1.9%)	2 (1.9%)
Investigations	臨床検査	1 (2.1%)	0	0	0
Liver function test increased	肝機能検査値上昇	1 (2.1%)	0	0	0

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験の肝機能障害関連有害事象の発現状況を表 2.7.4.2-37 に、肝機能障害関連有害事象に該当する各事象の発現割合を表 2.7.4.2-38 に示す。

肝機能障害関連有害事象は 3.8%に発現した。内訳は、肝機能異常(1.9%)、脂肪肝(0.9%)、アラニンアミノトランスフェラーゼ増加（0.9%)、アスパラギン酸アミノトランスフェラーゼ増加（0.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-37　肝機能障害関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Hepatic disorders)	1	(2.8%)	2	2	(5.4%)	2	1	(3.0%)	1	3	(4.3%)	3	4	(3.8%)	5
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Hepatic disorders) related to study drug	0			0			0			0			0		
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-38　肝機能障害関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Hepatic disorders		1 (2.8%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	4 (3.8%)
Hepatobiliary disorders	肝胆道系障害					
Hepatic function abnormal	肝機能異常	0	1 (2.7%)	1 (3.0%)	2 (2.9%)	2 (1.9%)
Hepatic steatosis	脂肪肝	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Investigations	臨床検査					
Alanine aminotransferase increased	アラニンアミノトランスフェラーゼ増加	1 (2.8%)	0	0	0	1 (0.9%)
Aspartate aminotransferase increased	アスパラギン酸アミノトランスフェラーゼ増加	1 (2.8%)	0	0	0	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.8　耐糖能異常関連

(1) 検証試験

耐糖能異常関連有害事象の発現状況を表 2.7.4.2-39、耐糖能異常関連有害事象に該当する各事象の発現割合を表 2.7.4.2-40 に示す。

耐糖能異常関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 6.4%、7.8%及び 3.8%に発現し、群間に大きな違いはなかった。実薬群で発現した有害事象は、口渇（2.1%、2.0%、1.9%）、体重増加（0%、3.9%、0%）、脱水（0%、0%、1.9%）、高トリグリセリド血症（0%、2.0%、0%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-39　耐糖能異常関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Hyperglycaemia/new onset diabetes mellitus)	3	(6.4%)	4	4	(7.8%)	5	2	(3.8%)	6	6	(5.8%)	11
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Hyperglycaemia/new onset diabetes mellitus) related to study drug	3	(6.4%)	4	3	(5.9%)	4	1	(1.9%)	2	4	(3.8%)	6
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-40　耐糖能異常関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Hyperglycaemia/new onset diabetes mellitus		3 (6.4%)	4 (7.8%)	2 (3.8%)	6 (5.8%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	1 (2.1%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Thirst	口渇	1 (2.1%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Investigations	臨床検査	1 (2.1%)	2 (3.9%)	0	2 (1.9%)
Weight increased	体重増加	0	2 (3.9%)	0	2 (1.9%)
Weight decreased	体重減少	1 (2.1%)	0	0	0
Metabolism and nutrition disorders	代謝および栄養障害	1 (2.1%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Dehydration	脱水	0	0	1 (1.9%)	1 (1.0%)
Hypertriglyceridaemia	高トリグリセリド血症	0	1 (2.0%)	0	1 (1.0%)
Increased appetite	食欲亢進	1 (2.1%)	0	0	0

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) **長期試験**

長期試験の耐糖能異常関連有害事象の発現状況を表 2.7.4.2-41 に、耐糖能異常関連有害事象に該当する各事象の発現割合を表 2.7.4.2-42 に示す。

耐糖能異常関連有害事象は17.9%に発現した。Overallで1%以上で発現した有害事象は、体重増加（14.2%）、脱水、高脂血症、食欲亢進（各 1.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-41　耐糖能異常関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Hyperglycaemia/new onset diabetes mellitus)	6	(16.7%)	7	7	(18.9%)	8	6	(18.2%)	10	13	(18.6%)	18	19	(17.9%)	25
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Hyperglycaemia/new onset diabetes mellitus) related to study drug	3	(8.3%)	3	4	(10.8%)	5	4	(12.1%)	4	8	(11.4%)	9	11	(10.4%)	12
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-42　耐糖能異常関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Hyperglycaemia/new onset diabetes mellitus		6 (16.7%)	7 (18.9%)	6 (18.2%)	13 (18.6%)	19 (17.9%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態					
Thirst	口渇	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Investigations	臨床検査					
Weight increased	体重増加	4 (11.1%)	7 (18.9%)	4 (12.1%)	11 (15.7%)	15 (14.2%)
Blood triglycerides increased	血中トリグリセリド増加	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Weight decreased	体重減少	1 (2.8%)	0	0	0	1 (0.9%)
Metabolism and nutrition disorders	代謝および栄養障害					
Dehydration	脱水	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Hyperlipidaemia	高脂血症	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Increased appetite	食欲亢進	2 (5.6%)	0	0	0	2 (1.9%)
Nervous system disorders	神経系障害					
Loss of consciousness	意識消失	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.9　自殺関連

(1) 検証試験

自殺関連有害事象は発現しなかった。

(2) 長期試験

長期試験の自殺関連有害事象の発現状況を表 2.7.4.2-43 に、自殺関連有害事象に該当する各事象の発現割合を表 2.7.4.2-44 に示す。

自殺関連有害事象は 6.6%に発現した。内訳は、故意の自傷行為(2.8%)、自殺既遂(1.9%)、自殺企図、自殺念慮（各 0.9%）であった。重篤な事象は自殺既遂が 2 名（1.9%)、自殺企図及び自殺念慮が各 1 名（各 0.9%）に発現した。自殺既遂及び自殺企図はいずれも投与中止に至り、重症度は重度であった。ほかに投与中止に至った有害事象及び重度の事象はなかった。

表 2.7.4.2-43　自殺関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Suicide/self-injury)	0			4	(10.8%)	4	3	(9.1%)	3	7	(10.0%)	7	7	(6.6%)	7
Death	0			0			2	(6.1%)	2	2	(2.9%)	2	2	(1.9%)	2
Serious	0			2	(5.4%)	2	2	(6.1%)	2	4	(5.7%)	4	4	(3.8%)	4
Leading to discontinuation	0			1	(2.7%)	1	2	(6.1%)	2	3	(4.3%)	3	3	(2.8%)	3
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			1	(2.7%)	1	1	(3.0%)	1	2	(2.9%)	2	2	(1.9%)	2
AE (Suicide/self-injury) related to study drug	0			0			1	(3.0%)	1	1	(1.4%)	1	1	(0.9%)	1
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			1	(3.0%)	1	1	(1.4%)	1	1	(0.9%)	1

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-44　自殺関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Suicide/self-injury		0	4 (10.8%)	3 (9.1%)	7 (10.0%)	7 (6.6%)
Psychiatric disorders	精神障害					
Intentional self-injury	故意の自傷行為	0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Completed suicide	自殺既遂	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Suicidal ideation	自殺念慮	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Suicide attempt	自殺企図	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.10 QT/QTc 間隔延長及び催不整脈作用関連

(1) 検証試験

QT/QTc 間隔延長及び催不整脈作用関連有害事象は発現しなかった。

(2) 長期試験

長期試験の QT/QTc 間隔延長及び催不整脈作用関連有害事象の発現状況を表 2.7.4.2-45 に、QT/QTc 間隔延長及び催不整脈作用関連有害事象に該当する各事象の発現割合を表 2.7.4.2-46 に示す。

QT/QTc 間隔延長及び催不整脈作用関連有害事象は 1.9%に発現した。内訳は、心電図 QT 延長、意識消失（各 0.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-45　QT/QTc 間隔延長及び催不整脈作用関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Torsade de pointes/QT prolongation)	0			0			2	(6.1%)	2	2	(2.9%)	2	2	(1.9%)	2
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Torsade de pointes/QT prolongation) related to study drug	0			0			1	(3.0%)	1	1	(1.4%)	1	1	(0.9%)	1
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-46　QT/QTc 間隔延長及び催不整脈作用関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Torsade de pointes/QT prolongation		0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Investigations	臨床検査					
Electrocardiogram QT prolonged	心電図ＱＴ延長	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Nervous system disorders	神経系障害					
Loss of consciousness	意識消失	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.11 中枢神経系

(1) 検証試験

中枢神経系有害事象の発現状況を表 2.7.4.2-47 に、中枢神経系有害事象に該当する各事象の発現割合を表 2.7.4.2-48 に示す。

中枢神経系有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 25.5%、51.0%及び 62.3%に発現し、プラセボ群と比べて 8 mg/日群及び 16 mg/日群で高かった。実薬合計で発現割合が 5%以上であった有害事象は、アカシジア（4.3%、13.7%、32.1%）、傾眠（2.1%、15.7%、18.9%）、頭痛（12.8%、11.8%、7.5%）、振戦（0%、9.8%、9.4%）、ジストニア（0%、2.0%、13.2%）、統合失調症（6.4%、7.8%、3.8%）であった。重篤な事象はなかった。投与中止に至った事象は、統合失調症［2 名（4.3%）、2 名（3.9%）、1 名（1.9%）］、傾眠［0 名、1 名（2.0%）、2 名（3.8%）］、アカシジア［0 名、0 名、1 名（1.9%）］、頭痛［1 名（2.1%）、0 名、0 名］であった。重度の事象は、統合失調症［2 名（4.3%）、1 名（2.0%）、1 名（1.9%）］、傾眠［0 名、0 名、1 名（1.9%）］であった。

表 2.7.4.2-47　中枢神経系有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Central nervous system)	12	(25.5%)	16	26	(51.0%)	49	33	(62.3%)	74	59	(56.7%)	123
Death	0			0			0			0		
Serious	1	(2.1%)	1	0			0			0		
Leading to discontinuation	3	(6.4%)	3	3	(5.9%)	3	4	(7.5%)	4	7	(6.7%)	7
AE (Central nervous system) related to study drug	7	(14.9%)	8	21	(41.2%)	40	30	(56.6%)	65	51	(49.0%)	105
Death	0			0			0			0		
Serious	1	(2.1%)	1	0			0			0		
Leading to discontinuation	3	(6.4%)	3	2	(3.9%)	2	3	(5.7%)	3	5	(4.8%)	5

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-48　中枢神経系有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Central nervous system		12 (25.5%)	26 (51.0%)	33 (62.3%)	59 (56.7%)
Nervous system disorders	神経系障害	9 (19.1%)	21 (41.2%)	32 (60.4%)	53 (51.0%)
Akathisia	アカシジア	2 (4.3%)	7 (13.7%)	17 (32.1%)	24 (23.1%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Somnolence	傾眠	1 (2.1%)	8 (15.7%)	10 (18.9%)	18 (17.3%)
Headache	頭痛	6 (12.8%)	6 (11.8%)	4 (7.5%)	10 (9.6%)
Tremor	振戦	0	5 (9.8%)	5 (9.4%)	10 (9.6%)
Dystonia	ジストニア	0	1 (2.0%)	7 (13.2%)	8 (7.7%)
Dyskinesia	ジスキネジア	0	0	3 (5.7%)	3 (2.9%)
Bradykinesia	運動緩慢	0	1 (2.0%)	1 (1.9%)	2 (1.9%)
Extrapyramidal disorder	錐体外路障害	0	1 (2.0%)	0	1 (1.0%)
Hypoaesthesia	感覚鈍麻	0	0	1 (1.9%)	1 (1.0%)
Myoclonus	ミオクローヌス	0	1 (2.0%)	0	1 (1.0%)
Parkinsonian gait	パーキンソン歩行	0	0	1 (1.9%)	1 (1.0%)
Dizziness	浮動性めまい	1 (2.1%)	0	0	0
Psychiatric disorders	精神障害	3 (6.4%)	6 (11.8%)	5 (9.4%)	11 (10.6%)
Schizophrenia	統合失調症	3 (6.4%)	4 (7.8%)	2 (3.8%)	6 (5.8%)
Insomnia	不眠症	0	0	2 (3.8%)	2 (1.9%)
Daydreaming	白日夢	0	1 (2.0%)	0	1 (1.0%)
Depression	うつ病	0	1 (2.0%)	0	1 (1.0%)
Dissociation	解離	0	0	1 (1.9%)	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験の中枢神経系有害事象の発現状況を表 2.7.4.2-49 に、中枢神経系有害事象に該当する各事象の発現割合を表 2.7.4.2-50 に示す。

中枢神経系有害事象は 58.5%に発現した。Overall で発現割合が 5%以上であった有害事象は、統合失調症（19.8%）、アカシジア（17.9%）、頭痛（17.0%）、振戦（17.0%）、ジストニア（11.3%）、傾眠（9.4%）であった。重篤な事象は、統合失調症 10 名（9.4%、うち 4 名が重度）、自殺既遂 2 名（1.9%、いずれも重度）、自殺企図（重度）、自殺念慮、衝動行為が各 1 名（各 0.9%）に発現した。重度の事象は、統合失調症 6 名（5.7%）、自殺既遂 2 名（1.9%）、自殺企図 1 名（0.9%）、攻撃性 1 名（0.9%）に発現し、統合失調症の 1 名を除き、いずれも投与中止となった。ほかに投与中止となった事象はなかった。

表 2.7.4.2-49　中枢神経系有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Central nervous system)	26	(72.2%)	64	23	(62.2%)	54	13	(39.4%)	39	36	(51.4%)	93	62	(58.5%)	157
Death	0			0			2	(6.1%)	2	2	(2.9%)	2	2	(1.9%)	2
Serious	7	(19.4%)	8	5	(13.5%)	5	3	(9.1%)	3	8	(11.4%)	8	15	(14.2%)	16
Leading to discontinuation	3	(8.3%)	3	3	(8.1%)	4	2	(6.1%)	2	5	(7.1%)	6	8	(7.5%)	9
Leading to dose decrease	9	(25.0%)	11	6	(16.2%)	8	4	(12.1%)	4	10	(14.3%)	12	19	(17.9%)	23
Leading to dose increase	1	(2.8%)	1	4	(10.8%)	4	5	(15.2%)	7	9	(12.9%)	11	10	(9.4%)	12
AE (Central nervous system) related to study drug	21	(58.3%)	39	18	(48.6%)	33	11	(33.3%)	20	29	(41.4%)	53	50	(47.2%)	92
Death	0			0			0			0			0		
Serious	0			1	(2.7%)	1	0			1	(1.4%)	1	1	(0.9%)	1
Leading to discontinuation	0			2	(5.4%)	2	0			2	(2.9%)	2	2	(1.9%)	2
Leading to dose decrease	9	(25.0%)	11	6	(16.2%)	8	4	(12.1%)	4	10	(14.3%)	12	19	(17.9%)	23
Leading to dose increase	0			1	(2.7%)	1	2	(6.1%)	3	3	(4.3%)	4	3	(2.8%)	4

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-50　中枢神経系有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Central nervous system		26 (72.2%)	23 (62.2%)	13 (39.4%)	36 (51.4%)	62 (58.5%)
Nervous system disorders	神経系障害					
Akathisia	アカシジア	6 (16.7%)	10 (27.0%)	3 (9.1%)	13 (18.6%)	19 (17.9%)
Headache	頭痛	6 (16.7%)	7 (18.9%)	5 (15.2%)	12 (17.1%)	18 (17.0%)
Tremor	振戦	9 (25.0%)	5 (13.5%)	4 (12.1%)	9 (12.9%)	18 (17.0%)
Dystonia	ジストニア	5 (13.9%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	12 (11.3%)
Somnolence	傾眠	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Dyskinesia	ジスキネジア	2 (5.6%)	2 (5.4%)	1 (3.0%)	3 (4.3%)	5 (4.7%)
Bradykinesia	運動緩慢	3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Dizziness	浮動性めまい	3 (8.3%)	0	1 (3.0%)	1 (1.4%)	4 (3.8%)
Hypoaesthesia	感覚鈍麻	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Loss of consciousness	意識消失	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Myoclonus	ミオクローヌス	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Psychiatric disorders	精神障害					
Schizophrenia	統合失調症	10 (27.8%)	5 (13.5%)	6 (18.2%)	11 (15.7%)	21 (19.8%)
Insomnia	不眠症	2 (5.6%)	1 (2.7%)	0	1 (1.4%)	3 (2.8%)
Intentional self-injury	故意の自傷行為	0	2 (5.4%)	1 (3.0%)	3 (4.3%)	3 (2.8%)
Completed suicide	自殺既遂	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Depressed mood	抑うつ気分	1 (2.8%)	1 (2.7%)	0	1 (1.4%)	2 (1.9%)
Aggression	攻撃性	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Autism spectrum disorder	自閉症スペクトラム障害	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Daydreaming	白日夢	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Disinhibition	脱抑制	1 (2.8%)	0	0	0	1 (0.9%)
Eating disorder	摂食障害	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Hallucination	幻覚	1 (2.8%)	0	0	0	1 (0.9%)
Impulsive behaviour	衝動行為	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Irritability	易刺激性	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Suicidal ideation	自殺念慮	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Suicide attempt	自殺企図	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.12 鎮静関連

(1) 検証試験

鎮静関連有害事象の発現状況を表 2.7.4.2-51 に、鎮静関連有害事象に該当する各事象の発現割合を表 2.7.4.2-52 に示す。

鎮静関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ2.1%、17.6%及び24.5%に発現し、プラセボ群と比べて 8 mg/日群及び 16 mg/日群で高かった。発現した有害事象は、傾眠（2.1%、15.7%、18.9%）、倦怠感（0%、2.0%、5.7%）、鎮静合併症（0%、0%、1.9%）であった。重篤な事象はなかった。投与中止に至った事象は傾眠が 8 mg/日群の 1 名（2.0%）、16 mg/日群の 2 名（3.8%、うち 1 名は重度）、倦怠感が16 mg/日群の 1 名（1.9%）に発現した。傾眠（16 mg/日群の 1 名）のほかに重度の事象はなかった。

表 2.7.4.2-51　鎮静関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Sedation)	1	(2.1%)	2	9	(17.6%)	14	13	(24.5%)	17	22	(21.2%)	31
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			1	(2.0%)	1	3	(5.7%)	3	4	(3.8%)	4
AE (Sedation) related to study drug	1	(2.1%)	1	7	(13.7%)	11	12	(22.6%)	16	19	(18.3%)	27
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			1	(2.0%)	1	3	(5.7%)	3	4	(3.8%)	4

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-52　鎮静関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Sedation		1 (2.1%)	9 (17.6%)	13 (24.5%)	22 (21.2%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態	0	1 (2.0%)	3 (5.7%)	4 (3.8%)
Malaise	倦怠感	0	1 (2.0%)	3 (5.7%)	4 (3.8%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	0	0	1 (1.9%)	1 (1.0%)
Sedation complication	鎮静合併症	0	0	1 (1.9%)	1 (1.0%)
Nervous system disorders	神経系障害	1 (2.1%)	8 (15.7%)	10 (18.9%)	18 (17.3%)
Somnolence	傾眠	1 (2.1%)	8 (15.7%)	10 (18.9%)	18 (17.3%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験の鎮静関連有害事象の発現状況を表 2.7.4.2-53 に、鎮静関連有害事象に該当する各事象の発現割合を表 2.7.4.2-54 に示す。

鎮静関連有害事象は 13.2%に発現した。内訳は、傾眠 (9.4%)、倦怠感 (2.8%)、疲労 (0.9%) であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-53　鎮静関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Sedation)	7	(19.4%)	9	4	(10.8%)	4	3	(9.1%)	3	7	(10.0%)	7	14	(13.2%)	16
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	7	(19.4%)	7	2	(5.4%)	2	1	(3.0%)	1	3	(4.3%)	3	10	(9.4%)	10
Leading to dose increase	0			0			0			0			0		
AE (Sedation) related to study drug	7	(19.4%)	9	4	(10.8%)	4	2	(6.1%)	2	6	(8.6%)	6	13	(12.3%)	15
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	7	(19.4%)	7	2	(5.4%)	2	1	(3.0%)	1	3	(4.3%)	3	10	(9.4%)	10
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-54　鎮静関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Sedation		7 (19.4%)	4 (10.8%)	3 (9.1%)	7 (10.0%)	14 (13.2%)
General disorders and administration site conditions	一般・全身障害および投与部位の状態					
Malaise	倦怠感	3 (8.3%)	0	0	0	3 (2.8%)
Fatigue	疲労	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Nervous system disorders	神経系障害					
Somnolence	傾眠	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.13 転倒・外傷関連

(1) 検証試験

転倒・外傷関連有害事象の発現状況を表 2.7.4.2-55 に、転倒・外傷関連有害事象に該当する各事象の発現割合を表 2.7.4.2-56 に示す。

転倒・外傷関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 12.8%、13.7%及び 17.0%に発現し、群間に大きな違いはなかった。実薬合計で発現割合が 5%以上であった有害事象は皮膚擦過傷（6.4%、3.9%、7.5%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-55　転倒・外傷関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Accidents and injuries)	6	(12.8%)	8	7	(13.7%)	14	9	(17.0%)	18	16	(15.4%)	32
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Accidents and injuries) related to study drug	0			0			0			0		
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-56　転倒・外傷関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Accidents and injuries		6 (12.8%)	7 (13.7%)	9 (17.0%)	16 (15.4%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症	6 (12.8%)	7 (13.7%)	9 (17.0%)	16 (15.4%)
Skin abrasion	皮膚擦過傷	3 (6.4%)	2 (3.9%)	4 (7.5%)	6 (5.8%)
Contusion	挫傷	2 (4.3%)	2 (3.9%)	3 (5.7%)	5 (4.8%)
Wound	創傷	0	1 (2.0%)	3 (5.7%)	4 (3.8%)
Ligament sprain	靭帯捻挫	1 (2.1%)	1 (2.0%)	1 (1.9%)	2 (1.9%)
Lip injury	口唇損傷	0	1 (2.0%)	0	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) **長期試験**

長期試験の転倒・外傷関連有害事象の発現状況を表 2.7.4.2-57 に、転倒・外傷関連有害事象に該当する各事象の発現割合を表 2.7.4.2-58 に示す。

転倒・外傷関連有害事象は 24.5%に発現した。Overall で発現割合が 5%以上であった有害事象は、皮膚擦過傷（10.4%）、創傷（7.5%）、挫傷（5.7%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-57　転倒・外傷関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Accidents and injuries)	7	(19.4%)	42	8	(21.6%)	14	11	(33.3%)	28	19	(27.1%)	42	26	(24.5%)	84
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Accidents and injuries) related to study drug	0			1	(2.7%)	1	0			1	(1.4%)	1	1	(0.9%)	1
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-58　転倒・外傷関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Accidents and injuries		7 (19.4%)	8 (21.6%)	11 (33.3%)	19 (27.1%)	26 (24.5%)
Injury, poisoning and procedural complications	傷害、中毒および処置合併症					
Skin abrasion	皮膚擦過傷	5 (13.9%)	3 (8.1%)	3 (9.1%)	6 (8.6%)	11 (10.4%)
Wound	創傷	3 (8.3%)	0	5 (15.2%)	5 (7.1%)	8 (7.5%)
Contusion	挫傷	1 (2.8%)	3 (8.1%)	2 (6.1%)	5 (7.1%)	6 (5.7%)
Ligament sprain	靭帯捻挫	2 (5.6%)	1 (2.7%)	2 (6.1%)	3 (4.3%)	5 (4.7%)
Thermal burn	熱傷	2 (5.6%)	0	0	0	2 (1.9%)
Burns second degree	第２度熱傷	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Forearm fracture	前腕骨折	1 (2.8%)	0	0	0	1 (0.9%)
Hand fracture	手骨折	1 (2.8%)	0	0	0	1 (0.9%)
Joint injury	関節損傷	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Lip injury	口唇損傷	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Mouth injury	口腔内損傷	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Nail avulsion	爪裂離	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Post-traumatic neck syndrome	外傷後頚部症候群	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.14 敵意・攻撃性関連

(1) 検証試験

敵意・攻撃性関連有害事象は、発現しなかった。

(2) 長期試験

長期試験の敵意・攻撃性関連有害事象の発現状況を表 2.7.4.2-59 に、敵意・攻撃性関連有害事象に該当する各事象の発現割合を表 2.7.4.2-60 に示す。

敵意・攻撃性関連有害事象は 3.8%に発現した。内訳は、攻撃性、脱抑制、衝動行為、易刺激性（各 0.9%）であった。重篤な事象は衝動行為が 1 名（0.9%）に発現した。投与中止に至った事象は攻撃性（重度）が 1 名（0.9%）に発現した。攻撃性（1 名）のほかに重度の事象はなかった。

表 2.7.4.2-59　敵意・攻撃性関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Hostility/aggression)	1	(2.8%)	1	3	(8.1%)	3	0			3	(4.3%)	3	4	(3.8%)	4
Death	0			0			0			0			0		
Serious	0			1	(2.7%)	1	0			1	(1.4%)	1	1	(0.9%)	1
Leading to discontinuation	0			1	(2.7%)	1	0			1	(1.4%)	1	1	(0.9%)	1
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Hostility/aggression) related to study drug	0			0			0			0			0		
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-60　敵意・攻撃性関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Hostility/aggression		1 (2.8%)	3 (8.1%)	0	3 (4.3%)	4 (3.8%)
Psychiatric disorders	精神障害					
Aggression	攻撃性	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Disinhibition	脱抑制	1 (2.8%)	0	0	0	1 (0.9%)
Impulsive behaviour	衝動行為	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Irritability	易刺激性	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.15 心血管系

(1) 検証試験

心血管系有害事象の発現状況を表 2.7.4.2-61 に、心血管系有害事象に該当する各事象の発現割合を表 2.7.4.2-62 に示す。

心血管系有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 0%、2.0%及び 1.9%に発現し、群間に大きな違いはなかった。発現した有害事象は、拡張期血圧低下（0%、2.0%、0%）、低血圧（0%、0%、1.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-61　心血管系有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Cardiac and vascular)	0			1	(2.0%)	2	1	(1.9%)	2	2	(1.9%)	4
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Cardiac and vascular) related to study drug	0			1	(2.0%)	2	1	(1.9%)	2	2	(1.9%)	4
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-62　心血管系有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Cardiac and vascular		0	1 (2.0%)	1 (1.9%)	2 (1.9%)
Investigations	臨床検査	0	1 (2.0%)	0	1 (1.0%)
Blood pressure diastolic decreased	拡張期血圧低下	0	1 (2.0%)	0	1 (1.0%)
Vascular disorders	血管障害	0	0	1 (1.9%)	1 (1.0%)
Hypotension	低血圧	0	0	1 (1.9%)	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) **長期試験**

長期試験の心血管系有害事象の発現状況を表 2.7.4.2-63 に、心血管系有害事象に該当する各事象の発現割合を表 2.7.4.2-64 に示す。

心血管系有害事象は 5.7%に発現した。内訳は、頻脈（1.9%）、徐脈、洞性頻脈、血圧上昇、心電図 QT 延長、低血圧（各 0.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-63　心血管系有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Cardiac and vascular)	1	(2.8%)	1	2	(5.4%)	3	3	(9.1%)	3	5	(7.1%)	6	6	(5.7%)	7
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Cardiac and vascular) related to study drug	1	(2.8%)	1	1	(2.7%)	1	2	(6.1%)	2	3	(4.3%)	3	4	(3.8%)	4
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-64　心血管系有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Cardiac and vascular		1 (2.8%)	2 (5.4%)	3 (9.1%)	5 (7.1%)	6 (5.7%)
Cardiac disorders	心臓障害					
Tachycardia	頻脈	1 (2.8%)	0	1 (3.0%)	1 (1.4%)	2 (1.9%)
Bradycardia	徐脈	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Sinus tachycardia	洞性頻脈	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Investigations	臨床検査					
Blood pressure increased	血圧上昇	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Electrocardiogram QT prolonged	心電図ＱＴ延長	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Vascular disorders	血管障害					
Hypotension	低血圧	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.16 プロラクチン増加関連

(1) 検証試験

プロラクチン増加関連有害事象の発現状況を表 2.7.4.2-65 に、プロラクチン増加関連有害事象に該当する各事象の発現割合を表 2.7.4.2-66 に示す。

プロラクチン増加関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 4.3%、15.7%及び 32.1%に発現し、プラセボ群と比べて 8 mg/日群及び 16 mg/日群で高かった。実薬合計で発現割合が 5%以上であった有害事象は、高プロラクチン血症（2.1%、9.8%、17.0%）、血中プロラクチン増加（2.1%、5.9%、13.2%）であった。重篤な事象及び重度の事象はなかった。投与中止に至った事象は血中プロラクチン増加(軽度)が 16 mg/日群の 1 名に発現した。

表 2.7.4.2-65　プロラクチン増加関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Prolactin)	2	(4.3%)	2	8	(15.7%)	15	17	(32.1%)	25	25	(24.0%)	40
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			1	(1.9%)	1	1	(1.0%)	1
AE (Prolactin) related to study drug	2	(4.3%)	2	8	(15.7%)	15	17	(32.1%)	25	25	(24.0%)	40
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			1	(1.9%)	1	1	(1.0%)	1

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-66　プロラクチン増加関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Prolactin Related AE		2 (4.3%)	8 (15.7%)	17 (32.1%)	25 (24.0%)
Endocrine disorders	内分泌障害	1 (2.1%)	5 (9.8%)	9 (17.0%)	14 (13.5%)
Hyperprolactinaemia	高プロラクチン血症	1 (2.1%)	5 (9.8%)	9 (17.0%)	14 (13.5%)
Investigations	臨床検査	1 (2.1%)	3 (5.9%)	7 (13.2%)	10 (9.6%)
Blood prolactin increased	血中プロラクチン増加	1 (2.1%)	3 (5.9%)	7 (13.2%)	10 (9.6%)
Reproductive system and breast disorders	生殖系および乳房障害	0	0	1 (1.9%)	1 (1.0%)
Galactorrhoea	乳汁漏出症	0	0	1 (1.9%)	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験のプロラクチン増加関連有害事象の発現状況を表 2.7.4.2-67 に、プロラクチン増加関連有害事象に該当する各事象の発現割合を表 2.7.4.2-68 に示す。

プロラクチン増加関連有害事象は 22.6%に発現した。Overall で発現割合が 5%以上であった有害事象は、高プロラクチン血症、血中プロラクチン増加（各 9.4%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-67　プロラクチン増加関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Prolactin)	9	(25.0%)	9	10	(27.0%)	10	5	(15.2%)	6	15	(21.4%)	16	24	(22.6%)	25
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Prolactin) related to study drug	8	(22.2%)	8	10	(27.0%)	10	5	(15.2%)	6	15	(21.4%)	16	23	(21.7%)	24
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-68　プロラクチン増加関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Prolactin AE		9 (25.0%)	10 (27.0%)	5 (15.2%)	15 (21.4%)	24 (22.6%)
Endocrine disorders	内分泌障害					
Hyperprolactinaemia	高プロラクチン血症	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Investigations	臨床検査					
Blood prolactin increased	血中プロラクチン増加	4 (11.1%)	4 (10.8%)	2 (6.1%)	6 (8.6%)	10 (9.4%)
Reproductive system and breast disorders	生殖系および乳房障害					
Menstruation irregular	不規則月経	1 (2.8%)	0	1 (3.0%)	1 (1.4%)	2 (1.9%)
Amenorrhoea-galactorrhoea syndrome	乳汁漏出無月経症候群	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Galactorrhoea	乳汁漏出症	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Abbreviations: AE, adverse event.
- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.17 体重増加関連

(1) 検証試験

体重増加関連有害事象の発現状況を表 2.7.4.2-69 に、体重増加関連有害事象に該当する各事象の発現割合を表 2.7.4.2-70 に示す。

体重増加関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 2.1%、3.9%及び 0%に発現し、群間に大きな違いはなかった。実薬群で発現した有害事象は体重増加（0%、3.9%、0%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-69　体重増加関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Weight increased)	1	(2.1%)	1	2	(3.9%)	3	0			2	(1.9%)	3
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Weight increased) related to study drug	1	(2.1%)	1	2	(3.9%)	3	0			2	(1.9%)	3
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-70　体重増加関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Weight increased		1 (2.1%)	2 (3.9%)	0	2 (1.9%)
Investigations	臨床検査	0	2 (3.9%)	0	2 (1.9%)
Weight increased	体重増加	0	2 (3.9%)	0	2 (1.9%)
Metabolism and nutrition disorders	代謝および栄養障害	1 (2.1%)	0	0	0
Increased appetite	食欲亢進	1 (2.1%)	0	0	0

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) **長期試験**

長期試験の体重増加関連有害事象の発現状況を表 2.7.4.2-71 に、体重増加関連有害事象に該当する各事象の発現割合を表 2.7.4.2-72 に示す。

体重増加関連有害事象は 17.0%に発現した。内訳は、体重増加（14.2%）、食欲亢進（1.9%）、摂食障害（0.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-71　体重増加関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Weight increased)	6	(16.7%)	6	7	(18.9%)	7	5	(15.2%)	5	12	(17.1%)	12	18	(17.0%)	18
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Weight increased) related to study drug	3	(8.3%)	3	4	(10.8%)	4	4	(12.1%)	4	8	(11.4%)	8	11	(10.4%)	11
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-72　体重増加関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Weight increased		6 (16.7%)	7 (18.9%)	5 (15.2%)	12 (17.1%)	18 (17.0%)
Investigations	臨床検査					
Weight increased	体重増加	4 (11.1%)	7 (18.9%)	4 (12.1%)	11 (15.7%)	15 (14.2%)
Metabolism and nutrition disorders	代謝および栄養障害					
Increased appetite	食欲亢進	2 (5.6%)	0	0	0	2 (1.9%)
Psychiatric disorders	精神障害					
Eating disorder	摂食障害	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.18 体重減少関連

(1) 検証試験

体重減少関連有害事象の発現状況を表 2.7.4.2-73 に、体重減少関連有害事象に該当する各事象の発現割合を表 2.7.4.2-74 に示す。

体重減少関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 2.1%、2.0%及び 0%に発現し、群間に大きな違いはなかった。実薬群で発現した有害事象は食欲減退（0%、2.0%、0%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-73　体重減少関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Weight decreased)	1	(2.1%)	1	1	(2.0%)	1	0			1	(1.0%)	1
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Weight decreased) related to study drug	1	(2.1%)	1	1	(2.0%)	1	0			1	(1.0%)	1
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-74　体重減少関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Weight decreased		1 (2.1%)	1 (2.0%)	0	1 (1.0%)
Investigations	臨床検査	1 (2.1%)	0	0	0
Weight decreased	体重減少	1 (2.1%)	0	0	0
Metabolism and nutrition disorders	代謝および栄養障害	0	1 (2.0%)	0	1 (1.0%)
Decreased appetite	食欲減退	0	1 (2.0%)	0	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) **長期試験**

長期試験の体重減少関連有害事象の発現状況を表 2.7.4.2-75 に、体重減少関連有害事象に該当する各事象の発現割合を表 2.7.4.2-76 に示す。

体重減少関連有害事象は 2.8%に発現した。内訳は、体重減少、食欲減退、拒食、摂食障害（各 0.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-75　体重減少関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Weight decreased)	2	(5.6%)	2	0			1	(3.0%)	2	1	(1.4%)	2	3	(2.8%)	4
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	1	(2.8%)	1	0			0			0			1	(0.9%)	1
Leading to dose increase	0			0			0			0			0		
AE (Weight decreased) related to study drug	1	(2.8%)	1	0			0			0			1	(0.9%)	1
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	1	(2.8%)	1	0			0			0			1	(0.9%)	1
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-76　体重減少関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Weight decreased		2 (5.6%)	0	1 (3.0%)	1 (1.4%)	3 (2.8%)
Investigations	臨床検査					
Weight decreased	体重減少	1 (2.8%)	0	0	0	1 (0.9%)
Metabolism and nutrition disorders	代謝および栄養障害					
Decreased appetite	食欲減退	1 (2.8%)	0	0	0	1 (0.9%)
Diet refusal	拒食	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)
Psychiatric disorders	精神障害					
Eating disorder	摂食障害	0	0	1 (3.0%)	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.19 脂質代謝異常関連

(1) 検証試験

脂質代謝異常関連有害事象の発現状況を表 2.7.4.2-77 に、脂質代謝異常関連有害事象に該当する各事象の発現割合を表 2.7.4.2-78 に示す。

脂質代謝異常関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 0%、3.9%及び 0%に発現し、群間に大きな違いはなかった。発現した有害事象は、脂質異常症（0%、2.0%、0%）、高トリグリセリド血症（0%、2.0%、0%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-77　脂質代謝異常関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Lipid metabolism disorder)	0			2	(3.9%)	2	0			2	(1.9%)	2
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Lipid metabolism disorder) related to study drug	0			0			0			0		
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-78　脂質代謝異常関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Lipid metabolism disorder		0	2 (3.9%)	0	2 (1.9%)
Metabolism and nutrition disorders	代謝および栄養障害	0	2 (3.9%)	0	2 (1.9%)
Dyslipidaemia	脂質異常症	0	1 (2.0%)	0	1 (1.0%)
Hypertriglyceridaemia	高トリグリセリド血症	0	1 (2.0%)	0	1 (1.0%)

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験の脂質代謝異常関連有害事象の発現状況を表 2.7.4.2-79 に、脂質代謝異常関連有害事象に該当する各事象の発現割合を表 2.7.4.2-80 に示す。

脂質代謝異常関連有害事象は 3.8%に発現した。内訳は、高脂血症（1.9%）、血中トリグリセリド増加、脂質異常症（各 0.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-79　脂質代謝異常関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Lipid metabolism disorder)	0			2	(5.4%)	2	2	(6.1%)	2	4	(5.7%)	4	4	(3.8%)	4
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Lipid metabolism disorder) related to study drug	0			2	(5.4%)	2	0			2	(2.9%)	2	2	(1.9%)	2
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-80　脂質代謝異常関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Lipid metabolism disorder		0	2 (5.4%)	2 (6.1%)	4 (5.7%)	4 (3.8%)
Investigations	臨床検査					
Blood triglycerides increased	血中トリグリセリド増加	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)
Metabolism and nutrition disorders	代謝および栄養障害					
Hyperlipidaemia	高脂血症	0	0	2 (6.1%)	2 (2.9%)	2 (1.9%)
Dyslipidaemia	脂質異常症	0	1 (2.7%)	0	1 (1.4%)	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.1.5.20 発育障害関連

(1) 検証試験

発育障害関連有害事象の発現状況を表 2.7.4.2-81 に、発育障害関連有害事象に該当する各事象の発現割合を表 2.7.4.2-82 に示す。

発育障害関連有害事象は、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 2.1%、3.9%及び 0%に発現し、群間に大きな違いはなかった。実薬群に発現した有害事象は体重増加（0%、3.9%、0%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-81　発育障害関連有害事象の発現状況（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47			8 MG N = 51			16 MG N = 53			Active N = 104		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Failure to thrive)	1	(2.1%)	1	2	(3.9%)	3	0			2	(1.9%)	3
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		
AE (Failure to thrive) related to study drug	1	(2.1%)	1	2	(3.9%)	3	0			2	(1.9%)	3
Death	0			0			0			0		
Serious	0			0			0			0		
Leading to discontinuation	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.2-82　発育障害関連有害事象の発現割合（検証試験、治療期）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Subjects with any Failure to thrive		1 (2.1%)	2 (3.9%)	0	2 (1.9%)
Investigations	臨床検査	1 (2.1%)	2 (3.9%)	0	2 (1.9%)
Weight increased	体重増加	0	2 (3.9%)	0	2 (1.9%)
Weight decreased	体重減少	1 (2.1%)	0	0	0

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

長期試験の発育障害関連有害事象の発現状況を表 2.7.4.2-83 に、発育障害関連有害事象に該当する各事象の発現割合を表 2.7.4.2-84 に示す。

発育関連有害事象は 14.2%に発現した。内訳は、体重増加（14.2%）、体重減少（0.9%）であった。重篤な事象、投与中止に至った事象及び重度の事象はなかった。

表 2.7.4.2-83　発育障害関連有害事象の発現状況（長期試験）

Safety Analysis Set

	DB-PLCB N = 36			DB-8MG N = 37			DB-16MG N = 33			DB-Active N = 70			Overall N = 106		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
AE (Failure to thrive)	4	(11.1%)	5	7	(18.9%)	7	4	(12.1%)	4	11	(15.7%)	11	15	(14.2%)	16
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		
AE (Failure to thrive) related to study drug	2	(5.6%)	2	4	(10.8%)	4	4	(12.1%)	4	8	(11.4%)	8	10	(9.4%)	10
Death	0			0			0			0			0		
Serious	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Leading to dose decrease	0			0			0			0			0		
Leading to dose increase	0			0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.2-84　発育障害関連有害事象の発現割合（長期試験）

Safety Analysis Set

System Organ Class Preferred Term	System Organ Class (J) Preferred Term (J)	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Subjects with any Failure to thrive		4 (11.1%)	7 (18.9%)	4 (12.1%)	11 (15.7%)	15 (14.2%)
Investigations	臨床検査					
Weight increased	体重増加	4 (11.1%)	7 (18.9%)	4 (12.1%)	11 (15.7%)	15 (14.2%)
Weight decreased	体重減少	1 (2.8%)	0	0	0	1 (0.9%)

- Adverse events are defined as adverse events with a start date on or after the date of first dose of extension study through the end date of follow-up phase.
- All adverse events were coded using MedDRA dictionary version 21.1.
- Although a subject may have had two or more adverse events, the subject is counted only once in a category per SOC and Preferred term. The same subject may appear in different categories per SOC and Preferred Term.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.2.2 個別有害事象の文章による説明

検証試験及び長期試験での死亡及びその他の重篤な有害事象の詳細をそれぞれ 2.7.6 項付録（2.7.6.1 項付録及び 2.7.6.2 項付録）に記載した。

2.7.4.3 臨床検査値の評価

2.7.4.3.1 治験期間を通しての臨床検査

(1) 検証試験

血清プロラクチン（女性）［Mean（SD）］が 6 週時 LOCF にプラセボ群と比べて 8 mg/日群及び 16 mg/日群で増加した。ベースラインはプラセボ群で 30.9（33.59） μg/L、8 mg/日群 34.8（37.04） μg/L、16 mg/日群 35.4（34.38） μg/L で、6 週時 LOCF のベースラインからの変化量はプラセボ群で−9.4（36.25） μg/L、8 mg/日群で 0.55（28.65） μg/L、16 mg/日群で 8.2（47.39） μg/L であった。血清プロラクチン（男性）では変動はみられなかった。その他、臨床検査値に特に変動はみられなかった。

なお、血清プロラクチン値で信頼性が担保されない 9 測定値（2.7.4.1.1.2.2 項参照）を除外したが、それらを含む集計と除外した集計で大きな違いはなかった（5.3.5.1.01 参照）。

(2) 長期試験

いずれの項目も DB ベースラインに比べて投与後に臨床的に問題となる変動はなかった。

2.7.4.3.2 個々の臨床的に重要な異常

検証試験及び長期試験のいずれでも、治験依頼者が臨床検査（血液生化学的検査、血液学的検査）ごとに設定した基準を超える値を顕著な異常値とした。

(1) 検証試験

顕著な異常値を示した被験者数を表 2.7.4.3-1 及び表 2.7.4.3-2 に示す。実薬合計で 2 名以上が顕著な異常値を示した項目は、血清プロラクチン高値（男性、女性）、ALT 高値、AST 高値、総コレステロール高値、CK 高値、空腹時トリグリセリド高値（女性）、好酸球高値、ヘマトクリット低値、ヘマトクリット高値、ヘモグロビン低値（女性）、ヘモグロビン高値であった。血清プロラクチン高値以外の顕著な異常値は、治験薬の投与を中止又は継続して軽快したこと、又は被験者の生理的変動、食事・運動の影響等による一過性のものであると考えられたことから、臨床的に問題となるものはないと考えられた。

なお、血清プロラクチン値で信頼性が担保されない測定値（2.7.4.1.1.2.2 項参照）のうち、顕著な異常に該当する被験者は 16 mg/日群の男性 1 名で、これを含めた集計と除外した集計で大きな違いはなかった（5.3.5.1.01 参照）。

表 2.7.4.3-1　顕著な異常値を示した被験者数（血液生化学的検査）（検証試験、治療期）

Safety Analysis Set

Parameter Criteria	PLCB N = 47 n/m (%)	8 MG N = 51 n/m (%)	16 MG N = 53 n/m (%)	Active N = 104 n/m (%)
Alanine Aminotransferase (U/L)				
Alanine Aminotransferase >= 2 x ULN	1/47 (2.1%)	2/49 (4.1%)	2/53 (3.8%)	4/102 (3.9%)
Alkaline Phosphatase (U/L)				
Alkaline Phosphatase >= 3 x ULN	0/47	0/49	0/53	0/102
Aspartate Aminotransferase (U/L)				
Aspartate Aminotransferase >= 2 x ULN	0/47	2/49 (4.1%)	0/53	2/102 (2.0%)
Bilirubin (mg/dL)				
Bilirubin >= 2.0 mg/dL	1/47 (2.1%)	0/49	0/53	0/102
Chloride (mEq/L)				
Chloride < 90 mEq/L	0/47	0/49	0/53	0/102
Chloride > 115 mEq/L	0/47	0/49	0/53	0/102
Cholesterol (mg/dL)				
Total Cholesterol (fasting) >= 240 mg/dL	1/46 (2.2%)	0/49	4/51 (7.8%)	4/100 (4.0%)
Creatine Kinase (U/L)				
Creatine Kinase >= 450 U/L	1/47 (2.1%)	3/49 (6.1%)	1/53 (1.9%)	4/102 (3.9%)
Creatinine (mg/dL)				
Creatinine >= 2.0 mg/dL	0/47	0/49	0/53	0/102
Gamma Glutamyl Transferase (U/L)				
Gamma Glutamyl Transferase >= 150 U/L	0/47	0/49	0/53	0/102
Glucose (mg/dL)				
Glucose (fasting or random) <= 45 mg/dL	0/47	0/49	0/53	0/102
Glucose (fasting) >= 126 mg/dL	0/46	0/49	0/51	0/100
Glucose (random) >= 200 mg/dL	0/47	0/49	0/53	0/102
Lactate Dehydrogenase (U/L)				
Lactate Dehydrogenase >= 3 x ULN	0/47	0/49	0/53	0/102
Potassium (mEq/L)				
Potassium <= 3 mEq/L	0/47	0/49	0/53	0/102

Parameter Criteria	PLCB N = 47 n/m (%)	8 MG N = 51 n/m (%)	16 MG N = 53 n/m (%)	Active N = 104 n/m (%)
Potassium >= 5.5 mEq/L	0/47	0/49	1/53 (1.9%)	1/102 (1.0%)
Prolactin (ug/L) (female)				
Prolactin >= 1 x ULN	7/27 (25.9%)	19/28 (67.9%)	20/30 (66.7%)	39/58 (67.2%)
Prolactin (ug/L) (male)				
Prolactin >= 1 x ULN	7/20 (35.0%)	18/21 (85.7%)	21/23 (91.3%)	39/44 (88.6%)
Sodium (mEq/L)				
Sodium <= 130 mEq/L	0/47	0/49	0/53	0/102
Sodium >= 150 mEq/L	0/47	0/49	0/53	0/102
Triglycerides (mg/dL)				
Triglycerides (fasting) >= 170 mg/dL	0/27	5/28 (17.9%)	1/30 (3.3%)	6/58 (10.3%)
Triglycerides (fasting) >= 200 mg/dL	1/19 (5.3%)	0/21	1/21 (4.8%)	1/42 (2.4%)
Urea Nitrogen (mg/dL)				
Urea Nitrogen >= 30 mg/dL	0/47	0/49	0/53	0/102

- Abbreviations: ULN, upper limit of the normal range.
- m is the total number of subjects with at least one post-baseline value.
- n and % are respectively the number and percentage of subjects meeting the specified criteria at least once post-baseline.
- m for "Total Cholesterol (fasting) >= 240 mg/dL" is the number of subjects with at least one post-baseline fasting total cholesterol value.
- m for "Triglycerides (fasting) >= 170 mg/dL" is the number of female subjects with at least one post-baseline fasting triglycerides value.
- m for "Triglycerides (fasting) >= 200 mg/dL" is the number of male subjects with at least one post-baseline fasting triglycerides value.
- Glucose (random): Glucose with any fasting status (fasting/non-fasting).
- m for "Glucose (fasting) >= 126 mg/dL" is the number of subjects with at least one post-baseline fasting glucose value.
- m for "Glucose (random) >= 200 mg/dL" is the number of subjects with at least one post-baseline fasting/non-fasting glucose value.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.3-2　顕著な異常値を示した被験者数（血液学的検査）（検証試験、治療期）

Safety Analysis Set

Parameter Criteria	PLCB N = 47 n/m (%)	8 MG N = 51 n/m (%)	16 MG N = 53 n/m (%)	Active N = 104 n/m (%)
Eosinophils/Leukocytes (%)				
Eosinophils/Leukocytes >= 10 %	0/47	3/49 (6.1%)	1/53 (1.9%)	4/102 (3.9%)
Erythrocytes (10^10/L)				
Erythrocytes <= 3.0 x 10^6/uL	0/47	0/49	0/53	0/102

Parameter Criteria	PLCB N = 47 n/m (%)	8 MG N = 51 n/m (%)	16 MG N = 53 n/m (%)	Active N = 104 n/m (%)
Erythrocytes >= 6.0 x 10^6/uL	0/47	1/49 (2.0%)	0/53	1/102 (1.0%)
Hematocrit (%)				
Hematocrit <= 30 %	0/47	1/49 (2.0%)	1/53 (1.9%)	2/102 (2.0%)
Hematocrit >= 50 %	2/47 (4.3%)	1/49 (2.0%)	1/53 (1.9%)	2/102 (2.0%)
Hemoglobin (g/dL)				
Hemoglobin <= 9.5 g/dL	1/27 (3.7%)	1/28 (3.6%)	1/30 (3.3%)	2/58 (3.4%)
Hemoglobin <= 11.5 g/dL	0/20	0/21	0/23	0/44
Hemoglobin >= 17.2 g/dL	1/47 (2.1%)	1/49 (2.0%)	1/53 (1.9%)	2/102 (2.0%)
Leukocytes (10^6/L)				
Leukocytes <= 2.8 x 10^3/uL	0/47	0/49	0/53	0/102
Leukocytes >= 16 x 10^3/uL	0/47	0/49	0/53	0/102
Neutrophils/Leukocytes (%)				
Neutrophils/Leukocytes <= 15 %	0/47	0/49	0/53	0/102
Platelets (10^10/L)				
Platelets <= 100 x 10^3/uL	0/47	0/49	0/53	0/102
Platelets >= 500 x 10^3/uL	0/47	0/49	0/53	0/102

- m is the total number of subjects with at least one post-baseline value.
- n and % are respectively the number and percentage of subjects meeting the specified criteria at least once post-baseline.
- m for "Hemoglobin <= 9.5 g/dL" is the number of female subjects with at least one post-baseline hemoglobin value.
- m for "Hemoglobin <= 11.5 g/dL" is the number of male subjects with at least one post-baseline hemoglobin value.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

顕著な異常値を示した被験者数を表 2.7.4.3-3 及び表 2.7.4.3-4 に示す。

Overall で2名以上に顕著な異常値がみられた臨床検査項目は、血清プロラクチン高値(男性、女性)、空腹時トリグリセライド高値（男性、女性)、ALT 高値、CK 高値、総コレステロール高値、好酸球高値、ヘマトクリット高値、ヘモグロビン高値、白血球低値、赤血球高値であった。

顕著な異常値がみられた臨床検査項目は、検証試験の実薬合計と長期試験の Overall で大きく変わらず、顕著な異常値の割合が検証試験と比べて長期試験で著しく増加することはなかった。

表 2.7.4.3-3　顕著な異常値を示した被験者数（血液生化学的検査）（長期試験）

Safety Analysis Set

Parameter Criteria	DB-PLCB N = 36 n/m (%)	DB-8MG N = 37 n/m (%)	DB-16MG N = 33 n/m (%)	DB-Active N = 70 n/m (%)	Overall N = 106 n/m (%)
Alanine Aminotransferase (U/L)					
Alanine Aminotransferase >= 2 x ULN	2/36 (5.6%)	4/37 (10.8%)	3/31 (9.7%)	7/68 (10.3%)	9/104 (8.7%)
Alkaline Phosphatase (U/L)					
Alkaline Phosphatase >= 3 x ULN	0/36	0/37	0/31	0/68	0/104
Aspartate Aminotransferase (U/L)					
Aspartate Aminotransferase >= 2 x ULN	0/36	1/37 (2.7%)	0/31	1/68 (1.5%)	1/104 (1.0%)
Bilirubin (mg/dL)					
Bilirubin >= 2.0 mg/dL	0/36	0/37	1/31 (3.2%)	1/68 (1.5%)	1/104 (1.0%)
Chloride (mEq/L)					
Chloride < 90 mEq/L	0/36	0/37	0/31	0/68	0/104
Chloride > 115 mEq/L	0/36	0/37	0/31	0/68	0/104
Cholesterol (mg/dL)					
Total Cholesterol (fasting) >= 240 mg/dL	2/35 (5.7%)	0/35	1/31 (3.2%)	1/66 (1.5%)	3/101 (3.0%)
Creatine Kinase (U/L)					
Creatine Kinase >= 450 U/L	3/36 (8.3%)	4/37 (10.8%)	1/31 (3.2%)	5/68 (7.4%)	8/104 (7.7%)
Creatinine (mg/dL)					
Creatinine >= 2.0 mg/dL	0/36	0/37	0/31	0/68	0/104
Gamma Glutamyl Transferase (U/L)					
Gamma Glutamyl Transferase >= 150 U/L	0/36	0/37	0/31	0/68	0/104
Glucose (mg/dL)					
Glucose (fasting or random) <= 45 mg/dL	0/36	0/37	0/31	0/68	0/104
Glucose (fasting) >= 126 mg/dL	0/35	0/35	0/31	0/66	0/101
Glucose (random) >= 200 mg/dL	0/36	0/37	0/31	0/68	0/104
Lactate Dehydrogenase (U/L)					
Lactate Dehydrogenase >= 3 x ULN	0/36	0/37	0/31	0/68	0/104

Parameter Criteria	DB-PLCB N = 36 n/m (%)	DB-8MG N = 37 n/m (%)	DB-16MG N = 33 n/m (%)	DB-Active N = 70 n/m (%)	Overall N = 106 n/m (%)
Potassium (mEq/L)					
Potassium <= 3 mEq/L	0/36	0/37	0/31	0/68	0/104
Potassium >= 5.5 mEq/L	0/36	0/37	0/31	0/68	0/104
Prolactin (ug/L) (female)					
Prolactin >= 1 x ULN	17/22 (77.3%)	16/21 (76.2%)	14/17 (82.4%)	30/38 (78.9%)	47/60 (78.3%)
Prolactin (ug/L) (male)					
Prolactin >= 1 x ULN	14/14 (100.0%)	14/16 (87.5%)	13/14 (92.9%)	27/30 (90.0%)	41/44 (93.2%)
Sodium (mEq/L)					
Sodium <= 130 mEq/L	0/36	0/37	0/31	0/68	0/104
Sodium >= 150 mEq/L	0/36	0/37	0/31	0/68	0/104
Triglycerides (mg/dL)					
Triglycerides (fasting) >= 170 mg/dL	5/22 (22.7%)	5/20 (25.0%)	2/17 (11.8%)	7/37 (18.9%)	12/59 (20.3%)
Triglycerides (fasting) >= 200 mg/dL	0/13	0/15	4/14 (28.6%)	4/29 (13.8%)	4/42 (9.5%)
Urea Nitrogen (mg/dL)					
Urea Nitrogen >= 30 mg/dL	0/36	0/37	0/31	0/68	0/104

- Abbreviations: ULN, upper limit of the normal range.
- m is the total number of subjects with at least one post-baseline value.
- n and % are respectively the number and percentage of subjects meeting the specified criteria at least once post-baseline.
- m for "Total Cholesterol (fasting) >= 240 mg/dL" is the number of subjects with at least one post-baseline fasting total cholesterol value.
- m for "Triglycerides (fasting) >= 170 mg/dL" is the number of female subjects with at least one post-baseline fasting triglycerides value.
- m for "Triglycerides (fasting) >= 200 mg/dL" is the number of male subjects with at least one post-baseline fasting triglycerides value.
- Glucose (random): Glucose with any fasting status (fasting/non-fasting).
- m for "Glucose (fasting) >= 126 mg/dL" is the number of subjects with at least one post-baseline fasting glucose value.
- m for "Glucose (random) >= 200 mg/dL" is the number of subjects with at least one post-baseline fasting/non-fasting glucose value.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.3-4　顕著な異常値を示した被験者数（血液学的検査）（長期試験）

Safety Analysis Set

Parameter Criteria	DB-PLCB N = 36 n/m (%)	DB-8MG N = 37 n/m (%)	DB-16MG N = 33 n/m (%)	DB-Active N = 70 n/m (%)	Overall N = 106 n/m (%)
Eosinophils/Leukocytes (%)					
Eosinophils/Leukocytes >= 10 %	3/36 (8.3%)	2/37 (5.4%)	2/31 (6.5%)	4/68 (5.9%)	7/104 (6.7%)
Erythrocytes (10^10/L)					
Erythrocytes <= 3.0 x 10^6/uL	0/36	0/37	0/31	0/68	0/104
Erythrocytes >= 6.0 x 10^6/uL	0/36	1/37 (2.7%)	1/31 (3.2%)	2/68 (2.9%)	2/104 (1.9%)
Hematocrit (%)					
Hematocrit <= 30 %	0/36	0/37	0/31	0/68	0/104
Hematocrit >= 50 %	2/36 (5.6%)	1/37 (2.7%)	3/31 (9.7%)	4/68 (5.9%)	6/104 (5.8%)
Hemoglobin (g/dL)					
Hemoglobin <= 9.5 g/dL	0/22	0/21	0/17	0/38	0/60
Hemoglobin <= 11.5 g/dL	0/14	0/16	0/14	0/30	0/44
Hemoglobin >= 17.2 g/dL	2/36 (5.6%)	2/37 (5.4%)	2/31 (6.5%)	4/68 (5.9%)	6/104 (5.8%)
Leukocytes (10^6/L)					
Leukocytes <= 2.8 x 10^3/uL	2/36 (5.6%)	1/37 (2.7%)	0/31	1/68 (1.5%)	3/104 (2.9%)
Leukocytes >= 16 x 10^3/uL	0/36	0/37	0/31	0/68	0/104
Neutrophils/Leukocytes (%)					
Neutrophils/Leukocytes <= 15 %	1/36 (2.8%)	0/37	0/31	0/68	1/104 (1.0%)
Platelets (10^10/L)					
Platelets <= 100 x 10^3/uL	0/36	0/37	1/31 (3.2%)	1/68 (1.5%)	1/104 (1.0%)
Platelets >= 500 x 10^3/uL	0/36	0/37	1/31 (3.2%)	1/68 (1.5%)	1/104 (1.0%)

- m is the total number of subjects with at least one post-baseline value.
- n and % are respectively the number and percentage of subjects meeting the specified criteria at least once post-baseline.
- m for "Hemoglobin <= 9.5 g/dL" is the number of female subjects with at least one post-baseline hemoglobin value.
- m for "Hemoglobin <= 11.5 g/dL" is the number of male subjects with at least one post-baseline hemoglobin value.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.4　バイタルサイン、身体的所見及び安全性に関連する他の観察項目

2.7.4.4.1　バイタルサイン

検証試験及び長期試験のいずれでも、治験依頼者がバイタルサイン（血圧、脈拍数、体温）ごとに設定した基準を超える値を顕著な異常値とした。

(1) 検証試験

顕著な異常値を示した被験者数を表 2.7.4.4-1 に示す。バイタルサイン（血圧、脈拍数、体温）の平均値は、いずれの群でも投与後にベースラインから大きく変動しなかった（5.3.5.1.01 参照）。バイタルサインの顕著な異常値を示した被験者の割合に群間で大きな違いはなかった。

表 2.7.4.4-1　顕著な異常値を示した被験者数（バイタルサイン）（検証試験、治療期）

Safety Analysis Set

Parameter Criteria	PLCB N = 47 n/m (%)	8 MG N = 51 n/m (%)	16 MG N = 53 n/m (%)	Active N = 104 n/m (%)
Diastolic Blood Pressure (mmHg)				
Diastolic Blood Pressure <= 50 and >= 15 decrease from baseline	3/47 (6.4%)	5/50 (10.0%)	4/52 (7.7%)	9/102 (8.8%)
Diastolic Blood Pressure >= 90 and >= 15 increase from baseline	2/47 (4.3%)	2/50 (4.0%)	3/52 (5.8%)	5/102 (4.9%)
Pulse Rate (beats/min)				
Pulse Rate <= 50 and >= 15 decrease from baseline	1/47 (2.1%)	1/51 (2.0%)	0/52	1/103 (1.0%)
Pulse Rate >= 120 and >= 15 increase from baseline	0/47	0/51	1/52 (1.9%)	1/103 (1.0%)
Systolic Blood Pressure (mmHg)				
Systolic Blood Pressure <= 90 and >= 20 decrease from baseline	2/47 (4.3%)	2/50 (4.0%)	3/52 (5.8%)	5/102 (4.9%)
Systolic Blood Pressure >= 135 and >= 20 increase from baseline	4/47 (8.5%)	3/50 (6.0%)	2/52 (3.8%)	5/102 (4.9%)
Temperature (C)				
Temperature >= 38.3 and >= 0.8 increase from baseline	0/47	0/51	0/52	0/103

- m is the total number of subjects with at least one post-baseline value.
- n and % are respectively the number and percentage of subjects meeting the specified criteria at least once post-baseline.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

顕著な異常値を示した被験者数を表 2.7.4.4-2 に示す。バイタルサイン（血圧、脈拍数、体温）の平均値は、いずれの項目も DB ベースラインから大きく変動しなかった（5.3.5.2.01 参照）。Overall（105 名）のうち、顕著な異常値を示した被験者は、拡張期血圧の低下 14.3%（15 名）及び上昇 14.3%（15 名）、脈拍数の減少 3.8%（4 名）及び増加 1.9%（2 名）、収縮期血圧の低下 5.7%（6 名）及び上昇 14.3%（15 名）であった。いずれも被験者の生理的変動又は一過性のものであると考えられた。

表 2.7.4.4-2　顕著な異常値を示した被験者数（バイタルサイン）（長期試験）

Safety Analysis Set

Parameter Criteria	DB-PLCB N = 36 n/m (%)	DB-8MG N = 37 n/m (%)	DB-16MG N = 33 n/m (%)	DB-Active N = 70 n/m (%)	Overall N = 106 n/m (%)
Diastolic Blood Pressure (mmHg)					
Diastolic Blood Pressure <= 50 and >= 15 decrease from baseline	2/36 (5.6%)	7/37 (18.9%)	6/32 (18.8%)	13/69 (18.8%)	15/105 (14.3%)
Diastolic Blood Pressure >= 90 and >= 15 increase from baseline	1/36 (2.8%)	5/37 (13.5%)	9/32 (28.1%)	14/69 (20.3%)	15/105 (14.3%)
Pulse Rate (beats/min)					
Pulse Rate <= 50 and >= 15 decrease from baseline	1/36 (2.8%)	2/37 (5.4%)	1/32 (3.1%)	3/69 (4.3%)	4/105 (3.8%)
Pulse Rate >= 120 and >= 15 increase from baseline	0/36	1/37 (2.7%)	1/32 (3.1%)	2/69 (2.9%)	2/105 (1.9%)
Systolic Blood Pressure (mmHg)					
Systolic Blood Pressure <= 90 and >= 20 decrease from baseline	2/36 (5.6%)	3/37 (8.1%)	1/32 (3.1%)	4/69 (5.8%)	6/105 (5.7%)
Systolic Blood Pressure >= 135 and >= 20 increase from baseline	3/36 (8.3%)	3/37 (8.1%)	9/32 (28.1%)	12/69 (17.4%)	15/105 (14.3%)
Temperature (C)					
Temperature >= 38.3 and >= 0.8 increase from baseline	0/36	0/37	0/32	0/69	0/105

- baseline: Baseline of confirmatory study.
- m is the total number of subjects with at least one post-baseline value.
- n and % are respectively the number and percentage of subjects meeting the specified criteria at least once post-baseline.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.4.2 体重、身長、BMI

体重及びBMIを検証試験及び長期試験で評価し、身長は長期試験のみで評価した。体重及び身長は、平均値の変動に加え、z-スコア及びパーセンタイルの変動を評価した（2.7.4.1.1.2.3 項参照）。

(1) 検証試験

ベースライン及び 6 週時（LOCF）の体重、体重 z-スコア及び体重パーセンタイルを表 2.7.4.4-3 に示す。体重及びBMIの平均値は、いずれの群でも投与後にベースラインからの大きな変動はなかった（5.3.5.1.01 参照）。いずれの群でも体重、体重 z-スコア及び体重パーセンタイルで、投与後にベースラインからの大きな変化はなかった。

表 2.7.4.4-3　ベースラインからの体重、体重 z-スコア及び体重パーセンタイル値の変化量（検証試験、治療期）

Safety Analysis Set

Parameter	Visit	PLCB N = 47		8 MG N = 51		16 MG N = 53		Active N = 104	
		Observed	Change	Observed	Change	Observed	Change	Observed	Change
Weight (kg)	Baseline								
	n	47		51		52		103	
	Mean (SD)	52.36 (7.943)		56.47 (11.951)		57.06 (11.671)		56.77 (11.756)	
	Median	51.40		53.40		54.85		54.60	
	Min, Max	38.0, 72.9		39.6, 89.7		39.5, 89.5		39.5, 89.7	
	Week 6 (LOCF)								
	n	47	47	50	50	53	52	103	102
	Mean (SD)	52.24 (8.082)	-0.12 (2.001)	56.72 (11.953)	0.13 (2.329)	57.03 (10.958)	-0.33 (2.404)	56.88 (11.396)	-0.10 (2.368)
	Median	50.30	0.20	55.40	0.00	55.20	-0.45	55.20	-0.20
	Min, Max	39.9, 75.4	-6.1, 3.6	38.9, 90.8	-6.0, 5.2	40.8, 87.5	-5.8, 4.1	38.9, 90.8	-6.0, 5.2
z-score of Weight	Baseline								
	n	47		51		52		103	
	Mean (SD)	-0.1982 (0.96628)		0.3266 (1.37238)		0.3347 (1.30122)		0.3307 (1.33036)	
	Median	-0.2685		-0.0916		0.1392		0.0651	
	Min, Max	-2.370, 2.319		-1.641, 3.289		-1.693, 4.767		-1.693, 4.767	
	Week 6 (LOCF)								
	n	47	47	50	50	53	52	103	102
	Mean (SD)	-0.2114 (0.96353)	-0.0132 (0.22656)	0.3509 (1.35701)	0.0124 (0.26274)	0.3493 (1.29350)	-0.0272 (0.26763)	0.3501 (1.31818)	-0.0078 (0.26468)
	Median	-0.2734	0.0258	-0.0201	-0.0016	0.0509	-0.0523	0.0000	-0.0198

Parameter	Visit	PLCB N = 47 Observed	Change	8 MG N = 51 Observed	Change	16 MG N = 53 Observed	Change	Active N = 104 Observed	Change
	Min, Max	-2.148, 2.686	-0.588, 0.422	-1.615, 3.230	-0.768, 0.586	-1.638, 4.444	-0.559, 0.430	-1.638, 4.444	-0.768, 0.586
Percentile of Weight	Baseline								
	n	47		51		52		103	
	Mean (SD)	48.01 (29.595)		56.92 (33.078)		59.69 (32.237)		58.32 (32.525)	
	Median	47.30		54.20		66.65		63.90	
	Min, Max	0.1, 97.3		2.4, 99.3		2.0, 99.7		2.0, 99.7	
	Week 6 (LOCF)								
	n	47	47	50	50	53	52	103	102
	Mean (SD)	46.76 (29.775)	-1.25 (8.384)	58.03 (32.397)	0.89 (8.899)	59.81 (33.005)	-0.62 (8.650)	58.94 (32.563)	0.12 (8.763)
	Median	48.60	0.00	58.30	0.00	62.80	0.00	60.30	0.00
	Min, Max	0.2, 98.3	-24.8, 12.8	3.6, 99.1	-23.5, 29.1	2.0, 99.7	-29.1, 18.8	2.0, 99.7	-29.1, 29.1

- Week 6 (LOCF) endpoint is the last post-baseline observation in the treatment phase up to 7 days after final date of the study drug, except for transition phase.
- At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute statistical summaries.
- z-score = (observed value - mean value of the reference population) / standard deviation value of reference population.
- Percentile of weight is calculated using "Trends in Average Weight by Age" in "Physical Development and Health of Students (2017)" statistics by Ministry of Education. Culture, Sports, Science and Technology.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

DB ベースラインからの体重及び身長の z-スコア及びパーセンタイルを表 2.7.4.4-4 及び表 2.7.4.4-5 に示す。体重［Mean（SD）］は最終評価時（LOCF）に DB ベースラインからの変化量が 2.75（5.379）kg であり大きな変動はなく、身長及び BMI の平均値も投与後に DB ベースラインからの大きな変動はなかった（5.3.5.2.01 参照）。体重及び身長の z-スコア及びパーセンタイル値のいずれでも DB ベースラインに比べて投与後に臨床的に問題となる変動はなかった。Overall（106 名）のうち、体重増加の有害事象を発現した被験者は 14.2%（15 名）（表 2.7.4.2-72）、体重減少は 0.9%（1 名）であった（表 2.7.4.2-76）。体重増加を発現した被験者のうち、DB ベースラインに比べ最終評価時（LOCF）の体重が 7%以上増加した被験者は 14 名であった。体重減少を発現した 1 名では、最終評価時（LOCF）に DB ベースラインからの変動は 7%未満であった。

表 2.7.4.4-4　ベースラインからの体重、体重 z-スコア及び体重パーセンタイル値の変化量（長期試験）

Safety Analysis Set

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
Weight (kg)	DB baseline										
	n	36		37		33		70		106	
	Mean (SD)	51.70 (7.674)		57.76 (11.371)		57.90 (11.781)		57.83 (11.482)		55.75 (10.713)	
	Median	51.20		56.70		55.80		56.25		53.50	
	Min, Max	38.0, 71.8		41.2, 85.6		39.5, 89.5		39.5, 89.5		38.0, 89.5	
	Day 1										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	51.88 (8.025)	0.18 (2.437)	58.62 (11.983)	0.86 (2.866)	57.98 (10.682)	0.08 (3.104)	58.32 (11.311)	0.49 (2.984)	56.13 (10.720)	0.39 (2.802)
	Median	50.70	0.15	57.00	1.00	56.20	0.80	56.55	0.95	54.05	0.80
	Min, Max	40.6, 75.6	-5.9, 4.0	41.1, 91.8	-8.6, 6.2	43.4, 85.5	-7.4, 4.7	41.1, 91.8	-8.6, 6.2	40.6, 91.8	-8.6, 6.2
	Week 28										
	n	28	28	28	28	25	25	53	53	81	81
	Mean (SD)	55.28 (9.543)	2.96 (4.593)	58.91 (10.009)	3.56 (3.360)	59.64 (11.055)	1.51 (5.150)	59.25 (10.419)	2.60 (4.379)	57.88 (10.243)	2.72 (4.429)
	Median	53.10	2.65	58.80	3.55	56.80	0.80	57.60	2.20	55.30	2.50
	Min, Max	40.7, 86.9	-5.9, 15.1	45.1, 80.6	-1.3, 13.7	44.9, 90.2	-8.9, 15.3	44.9, 90.2	-8.9, 15.3	40.7, 90.2	-8.9, 15.3
	Week 52										
	n	22	22	23	23	18	18	41	41	63	63

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
	Mean (SD)	55.17 (10.219)	3.04 (5.595)	57.90 (11.130)	3.34 (5.466)	63.96 (15.096)	4.03 (6.175)	60.56 (13.201)	3.65 (5.723)	58.68 (12.431)	3.43 (5.641)
	Median	54.00	2.30	55.80	1.80	59.55	2.75	59.30	1.90	55.90	2.10
	Min, Max	40.2, 89.0	-8.9, 17.2	40.8, 81.8	-3.2, 18.3	46.0, 107.6	-2.5, 18.1	40.8, 107.6	-3.2, 18.3	40.2, 107.6	-8.9, 18.3
	LOCF endpoint										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	54.35 (9.366)	2.65 (5.510)	61.12 (13.106)	3.36 (5.273)	60.08 (12.986)	2.18 (5.449)	60.63 (12.966)	2.81 (5.350)	58.50 (12.192)	2.75 (5.379)
	Median	53.70	1.90	59.80	2.50	58.00	1.40	58.55	2.05	55.80	2.05
	Min, Max	40.2, 89.0	-8.9, 17.2	40.8, 96.6	-9.8, 18.3	44.9, 107.6	-6.6, 18.1	40.8, 107.6	-9.8, 18.3	40.2, 107.6	-9.8, 18.3
Percentile of Weight	DB baseline										
	n	36		37		33		70		106	
	Mean (SD)	47.87 (28.510)		60.94 (32.267)		63.33 (32.573)		62.07 (32.198)		57.24 (31.589)	
	Median	49.85		69.10		75.10		72.00		60.30	
	Min, Max	0.1, 97.3		5.6, 99.3		2.0, 99.7		2.0, 99.7		0.1, 99.7	
	Day 1										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	46.96 (28.773)	-0.91 (9.966)	61.97 (31.615)	1.04 (12.476)	63.70 (32.316)	0.37 (11.274)	62.79 (31.727)	0.72 (11.843)	57.41 (31.530)	0.17 (11.219)
	Median	47.55	0.00	63.90	0.70	74.70	0.00	66.40	0.50	58.30	0.00
	Min, Max	0.3, 98.3	-31.2, 14.4	5.1, 99.3	-38.8, 34.1	2.0, 99.7	-37.4, 19.2	2.0, 99.7	-38.8, 34.1	0.3, 99.7	-38.8, 34.1

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
	Week 28										
	n	28	28	28	28	25	25	53	53	81	81
	Mean (SD)	59.96 (26.472)	8.37 (16.252)	66.78 (29.001)	9.03 (12.556)	68.70 (30.951)	2.77 (16.881)	67.68 (29.661)	6.08 (14.945)	65.01 (28.670)	6.87 (15.347)
	Median	61.55	4.60	75.10	8.60	80.80	0.10	78.50	4.70	70.50	4.70
	Min, Max	0.2, 99.6	-31.2, 38.1	12.4, 99.5	-26.5, 42.1	3.9, 99.8	-41.1, 50.2	3.9, 99.8	-41.1, 50.2	0.2, 99.8	-41.1, 50.2
	Week 52										
	n	22	22	23	23	18	18	41	41	63	63
	Mean (SD)	61.40 (29.944)	9.03 (21.640)	61.95 (31.492)	7.69 (15.956)	74.59 (28.460)	5.16 (14.099)	67.50 (30.496)	6.58 (15.038)	65.37 (30.204)	7.43 (17.490)
	Median	71.05	6.95	73.50	5.00	86.15	0.40	78.50	2.60	73.80	3.00
	Min, Max	0.2, 99.6	-48.5, 49.7	3.6, 99.4	-31.6, 42.1	12.4, 100.0	-9.2, 52.5	3.6, 100.0	-31.6, 52.5	0.2, 100.0	-48.5, 52.5
	LOCF endpoint										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	54.68 (31.341)	6.81 (19.845)	67.27 (31.347)	6.34 (16.285)	66.32 (31.513)	2.99 (13.118)	66.83 (31.200)	4.76 (14.866)	62.70 (31.631)	5.46 (16.657)
	Median	56.45	3.90	75.70	4.10	80.80	0.50	79.65	1.55	72.45	2.45
	Min, Max	0.2, 99.6	-48.5, 49.7	3.4, 99.7	-43.3, 42.1	3.9, 100.0	-25.2, 52.5	3.4, 100.0	-43.3, 52.5	0.2, 100.0	-48.5, 52.5
z-score of Weight	DB baseline										
	n	36		37		33		70		106	
	Mean (SD)	-0.2292 (0.94468)		0.4785 (1.38627)		0.4829 (1.39803)		0.4806 (1.38169)		0.2395 (1.29077)	

Parameter	Visit	DB-PLCB N = 36		DB-8MG N = 37		DB-16MG N = 33		DB-Active N = 70		Overall N = 106	
		Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change
	Median	-0.2430		0.2144		0.4161		0.2972		-0.0195	
	Min, Max	-2.370, 2.319		-1.473, 3.289		-1.693, 4.767		-1.693, 4.767		-2.370, 4.767	
	Day 1										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	-0.2263 (0.95929)	0.0029 (0.27331)	0.5508 (1.44147)	0.0723 (0.33556)	0.4610 (1.29958)	-0.0219 (0.38121)	0.5085 (1.36726)	0.0279 (0.35831)	0.2589 (1.28742)	0.0194 (0.33077)
	Median	-0.2917	0.0047	0.0268	0.1302	0.4167	0.0385	0.1029	0.0950	-0.0521	0.0388
	Min, Max	-2.071, 2.706	-0.754, 0.517	-1.522, 3.529	-0.838, 0.776	-1.638, 4.156	-0.772, 0.520	-1.638, 4.156	-0.838, 0.776	-2.071, 4.156	-0.838, 0.776
	Week 28										
	n	28	28	28	28	25	25	53	53	81	81
	Mean (SD)	0.2123 (1.15934)	0.3303 (0.53453)	0.6646 (1.36648)	0.3895 (0.41902)	0.7013 (1.37124)	0.1450 (0.55244)	0.6819 (1.35563)	0.2741 (0.49720)	0.5196 (1.30332)	0.2936 (0.50778)
	Median	0.0245	0.2963	0.3551	0.4036	0.6104	0.0589	0.5493	0.2416	0.2474	0.2601
	Min, Max	-2.110, 3.856	-0.754, 1.654	-1.050, 3.737	-0.580, 1.394	-1.416, 4.757	-0.857, 1.590	-1.416, 4.757	-0.857, 1.590	-2.110, 4.757	-0.857, 1.654
	Week 52										
	n	22	22	23	23	18	18	41	41	63	63
	Mean (SD)	0.2318 (1.23155)	0.3530 (0.65765)	0.4531 (1.35149)	0.3250 (0.60257)	1.1689 (1.85088)	0.4216 (0.70684)	0.7674 (1.60932)	0.3674 (0.64374)	0.5803 (1.50029)	0.3624 (0.64335)
	Median	0.2644	0.2128	0.3271	0.1754	0.8317	0.2426	0.5469	0.1830	0.3356	0.2119
	Min, Max	-2.158, 4.069	-1.138, 1.750	-1.525, 3.773	-0.692, 1.760	-1.108, 6.982	-0.241, 2.215	-1.525, 6.982	-0.692, 2.215	-2.158, 6.982	-1.138, 2.215

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
	LOCF endpoint										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	0.0718 (1.18644)	0.3010 (0.63478)	0.8260 (1.57702)	0.3475 (0.57454)	0.6947 (1.61075)	0.2118 (0.63522)	0.7641 (1.58278)	0.2835 (0.60333)	0.5290 (1.49131)	0.2895 (0.61122)
	Median	-0.0645	0.2046	0.3899	0.2763	0.6002	0.1322	0.5481	0.2426	0.2983	0.2083
	Min, Max	-2.158, 4.069	-1.138, 1.750	-1.547, 3.947	-0.955, 1.760	-1.484, 6.982	-0.772, 2.215	-1.547, 6.982	-0.955, 2.215	-2.158, 6.982	-1.138, 2.215
Body Mass Index (kg/m2)	DB baseline										
	n	36		37		33		70		106	
	Mean (SD)	19.99 (2.358)		22.12 (3.723)		21.97 (3.966)		22.05 (3.812)		21.35 (3.517)	
	Median	20.03		21.12		21.84		21.46		20.73	
	Min, Max	15.2, 25.8		15.9, 30.1		15.8, 36.5		15.8, 36.5		15.2, 36.5	
	Day 1										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	19.99 (2.462)	0.00 (0.932)	22.33 (3.879)	0.21 (1.095)	22.03 (3.711)	0.06 (1.206)	22.19 (3.776)	0.14 (1.143)	21.44 (3.534)	0.09 (1.073)
	Median	19.83	0.04	20.99	0.23	21.30	0.14	21.03	0.22	20.58	0.14
	Min, Max	16.1, 25.9	-2.2, 1.6	16.4, 30.7	-3.0, 2.1	16.2, 34.8	-2.5, 2.1	16.2, 34.8	-3.0, 2.1	16.1, 34.8	-3.0, 2.1
	Week 28										
	n	28	28	28	28	25	25	53	53	81	81
	Mean (SD)	21.26 (2.862)	0.94 (1.640)	22.44 (3.653)	0.95 (1.161)	22.78 (4.067)	0.50 (1.913)	22.60 (3.820)	0.74 (1.562)	22.14 (3.558)	0.81 (1.582)

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
	Median	20.73	0.95	21.44	0.96	22.49	0.23	21.52	0.56	21.38	0.66
	Min, Max	16.2, 28.2	-2.2, 4.6	16.7, 31.6	-1.6, 3.5	18.3, 35.9	-2.8, 5.4	16.7, 35.9	-2.8, 5.4	16.2, 35.9	-2.8, 5.4
	Week 52										
	n	22	22	23	23	18	18	41	41	63	63
	Mean (SD)	21.20 (3.137)	0.94 (2.079)	21.79 (3.546)	0.81 (1.819)	23.94 (5.768)	1.30 (2.285)	22.73 (4.713)	1.03 (2.024)	22.20 (4.267)	1.00 (2.027)
	Median	20.86	0.73	21.05	0.67	22.72	0.47	21.97	0.55	21.64	0.67
	Min, Max	15.9, 28.7	-3.5, 4.8	16.8, 31.9	-2.6, 5.6	17.8, 43.2	-0.9, 6.7	16.8, 43.2	-2.6, 6.7	15.9, 43.2	-3.5, 6.7
	LOCF endpoint										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	20.81 (3.085)	0.82 (2.044)	23.03 (4.162)	0.91 (1.762)	22.80 (4.790)	0.83 (1.960)	22.92 (4.437)	0.87 (1.844)	22.20 (4.138)	0.85 (1.905)
	Median	20.20	0.46	21.66	0.88	22.40	0.39	22.02	0.72	21.47	0.68
	Min, Max	15.9, 28.7	-3.5, 4.8	16.8, 31.9	-3.4, 5.6	17.3, 43.2	-2.3, 6.7	16.8, 43.2	-3.4, 6.7	15.9, 43.2	-3.5, 6.7

- DB baseline: Baseline of confirmatory study.
- At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute statistical summaries.
- Percentile of weight is calculated using "Trends in Average Weight by Age" in "Physical Development and Health of Students (2017)" statistics by Ministry of Education. Culture, Sports, Science and Technology.
- z-score = (observed value - mean value of the reference population) / standard deviation value of reference population.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.4-5　ベースラインからの身長、身長 z-スコア及び身長パーセンタイル値の変化量（長期試験）

Safety Analysis Set

		DB-PLCB N = 36		DB-8MG N = 37		DB-16MG N = 33		DB-Active N = 70		Overall N = 106	
Parameter	Visit	Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change
Height (cm)	DB baseline										
	n	36		37		33		70		106	
	Mean (SD)	160.67 (6.531)		161.32 (6.999)		162.13 (7.678)		161.70 (7.285)		161.35 (7.024)	
	Median	160.90		161.80		161.40		161.45		161.15	
	Min, Max	144.9, 173.5		148.0, 179.6		147.3, 181.8		147.3, 181.8		144.9, 181.8	
	Day 1										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	160.96 (6.803)	0.29 (0.943)	161.72 (6.810)	0.40 (0.943)	162.16 (7.491)	0.04 (0.682)	161.93 (7.090)	0.23 (0.844)	161.60 (6.976)	0.25 (0.875)
	Median	161.80	0.00	162.00	0.20	161.60	0.10	161.65	0.20	161.70	0.10
	Min, Max	145.0, 176.2	-1.9, 2.7	148.0, 179.0	-1.5, 3.6	147.5, 181.3	-1.5, 1.2	147.5, 181.3	-1.5, 3.6	145.0, 181.3	-1.9, 3.6
	Week 28										
	n	36	36	35	35	29	29	64	64	100	100
	Mean (SD)	161.40 (6.875)	0.73 (1.056)	161.88 (6.545)	1.28 (1.761)	161.57 (7.309)	-0.11 (2.165)	161.74 (6.847)	0.65 (2.060)	161.62 (6.824)	0.68 (1.759)
	Median	161.80	0.50	161.90	0.50	161.00	0.40	161.40	0.50	161.40	0.50
	Min, Max	144.4, 175.5	-0.6, 4.0	148.1, 174.5	-0.3, 6.4	147.3, 182.5	-7.0, 3.3	147.3, 182.5	-7.0, 6.4	144.4, 182.5	-7.0, 6.4
	Week 52										
	n	26	26	26	26	19	19	45	45	71	71

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
	Mean (SD)	161.28 (7.417)	1.08 (1.429)	162.18 (7.122)	1.47 (1.835)	163.52 (7.741)	1.04 (1.538)	162.75 (7.333)	1.28 (1.711)	162.21 (7.345)	1.21 (1.606)
	Median	161.80	0.75	163.00	1.00	162.70	1.00	162.80	1.00	162.80	0.90
	Min, Max	146.0, 176.2	-1.1, 6.0	148.1, 173.5	-0.7, 6.9	146.7, 183.3	-1.3, 5.4	146.7, 183.3	-1.3, 6.9	146.0, 183.3	-1.3, 6.9
	LOCF endpoint										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	161.56 (7.088)	0.89 (1.324)	162.55 (7.162)	1.23 (1.871)	162.34 (7.224)	0.21 (2.230)	162.45 (7.140)	0.75 (2.097)	162.15 (7.101)	0.80 (1.865)
	Median	161.80	0.65	162.40	0.50	162.00	0.30	162.35	0.45	162.35	0.50
	Min, Max	146.0, 176.2	-1.1, 6.0	148.1, 179.0	-0.7, 6.9	146.7, 183.3	-7.0, 5.4	146.7, 183.3	-7.0, 6.9	146.0, 183.3	-7.0, 6.9
Percentile of Height	DB baseline										
	n	36		37		33		70		106	
	Mean (SD)	52.98 (31.068)		55.11 (28.345)		55.93 (30.067)		55.50 (28.959)		54.64 (29.568)	
	Median	53.50		51.60		51.60		51.60		51.60	
	Min, Max	0.1, 99.4		4.4, 97.3		1.3, 100.0		1.3, 100.0		0.1, 100.0	
	Day 1										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	54.63 (32.112)	1.64 (4.647)	55.58 (28.938)	0.46 (4.827)	55.68 (30.599)	-0.25 (4.712)	55.63 (29.515)	0.13 (4.752)	55.29 (30.272)	0.64 (4.749)
	Median	59.15	0.00	54.70	0.00	50.20	0.00	51.60	0.00	55.50	0.00
	Min, Max	0.1, 99.3	-6.7, 15.0	4.4, 97.3	-13.0, 10.8	1.3, 99.9	-17.2, 7.4	1.3, 99.9	-17.2, 10.8	0.1, 99.9	-17.2, 15.0

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
	Week 28										
	n	36	36	35	35	29	29	64	64	100	100
	Mean (SD)	56.40 (31.411)	3.42 (5.530)	59.30 (27.964)	4.97 (7.789)	54.42 (30.771)	0.96 (8.656)	57.09 (29.135)	3.15 (8.372)	56.84 (29.818)	3.25 (7.445)
	Median	56.65	0.00	67.80	1.20	57.00	0.00	59.80	0.30	58.30	0.00
	Min, Max	0.1, 99.0	-6.7, 16.8	6.5, 97.3	-5.1, 30.8	0.2, 100.0	-28.8, 13.4	0.2, 100.0	-28.8, 30.8	0.1, 100.0	-28.8, 30.8
	Week 52										
	n	26	26	26	26	19	19	45	45	71	71
	Mean (SD)	55.64 (31.825)	4.58 (6.473)	59.74 (29.010)	5.72 (8.127)	58.81 (31.821)	3.65 (8.455)	59.35 (29.877)	4.84 (8.236)	57.99 (30.431)	4.75 (7.591)
	Median	53.45	3.80	65.05	5.35	67.90	2.60	65.50	4.50	62.60	3.90
	Min, Max	2.6, 99.3	-6.7, 21.4	6.5, 98.4	-7.2, 30.8	4.5, 100.0	-17.2, 21.5	4.5, 100.0	-17.2, 30.8	2.6, 100.0	-17.2, 30.8
	LOCF endpoint										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	57.11 (32.084)	4.12 (6.054)	59.71 (28.530)	4.59 (7.743)	57.45 (31.010)	1.52 (9.158)	58.64 (29.529)	3.14 (8.519)	58.12 (30.276)	3.48 (7.754)
	Median	61.95	3.20	64.60	2.10	58.30	0.00	62.95	1.05	61.95	1.55
	Min, Max	0.1, 99.3	-6.7, 21.4	6.5, 98.4	-7.2, 30.8	0.2, 100.0	-28.8, 21.5	0.2, 100.0	-28.8, 30.8	0.1, 100.0	-28.8, 30.8
z-score of Height	DB baseline										
	n	36		37		33		70		106	

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
	Mean (SD)	-0.0796 (1.17105)		0.0000 (0.91293)		0.1338 (1.22032)		0.0631 (1.06302)		0.0146 (1.09741)	
	Median	-0.0214		-0.0672		-0.1176		-0.0924		-0.0649	
	Min, Max	-3.237, 2.368		-1.765, 1.767		-2.470, 3.327		-2.470, 3.327		-3.237, 3.327	
	Day 1										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	-0.0463 (1.19360)	0.0332 (0.17099)	0.0329 (0.92884)	0.0329 (0.18213)	0.1101 (1.20830)	-0.0237 (0.17258)	0.0693 (1.06242)	0.0062 (0.17869)	0.0300 (1.10438)	0.0154 (0.17577)
	Median	0.0291	0.0000	-0.0513	0.0131	-0.0672	0.0000	-0.0636	0.0032	-0.0406	0.0000
	Min, Max	-3.288, 2.118	-0.493, 0.432	-1.765, 1.861	-0.539, 0.539	-2.470, 3.199	-0.602, 0.204	-2.470, 3.199	-0.602, 0.539	-3.288, 3.199	-0.602, 0.539
	Week 28										
	n	36	36	35	35	29	29	64	64	100	100
	Mean (SD)	0.0302 (1.20668)	0.1098 (0.17026)	0.1338 (0.91030)	0.1719 (0.25581)	0.0200 (1.25728)	-0.0530 (0.38530)	0.0823 (1.07379)	0.0700 (0.33768)	0.0635 (1.11765)	0.0844 (0.28841)
	Median	0.0528	0.0800	0.2051	0.0938	0.0150	0.0562	0.0597	0.0667	0.0596	0.0708
	Min, Max	-3.339, 2.279	-0.102, 0.545	-1.746, 1.861	-0.209, 0.958	-2.998, 3.346	-1.313, 0.413	-2.998, 3.346	-1.313, 0.958	-3.339, 3.346	-1.313, 0.958
	Week 52										
	n	26	26	26	26	19	19	45	45	71	71
	Mean (SD)	0.0834 (1.16952)	0.1593 (0.21944)	0.1550 (0.95505)	0.1909 (0.21785)	0.2649 (1.30624)	0.1261 (0.26668)	0.2014 (1.10421)	0.1635 (0.23897)	0.1582 (1.12168)	0.1620 (0.23043)
	Median	-0.0064	0.1109	0.2227	0.1670	0.2994	0.1501	0.2574	0.1501	0.1681	0.1472
	Min, Max	-1.993, 2.279	-0.202, 0.784	-1.746, 2.049	-0.131, 0.745	-1.835, 3.474	-0.485, 0.675	-1.835, 3.474	-0.485, 0.745	-1.993, 3.474	-0.485, 0.784

Parameter	Visit	DB-PLCB N = 36 Observed	DB-PLCB N = 36 Change	DB-8MG N = 37 Observed	DB-8MG N = 37 Change	DB-16MG N = 33 Observed	DB-16MG N = 33 Change	DB-Active N = 70 Observed	DB-Active N = 70 Change	Overall N = 106 Observed	Overall N = 106 Change
	LOCF endpoint										
	n	36	36	37	37	33	33	70	70	106	106
	Mean (SD)	0.0536 (1.23300)	0.1332 (0.20444)	0.1605 (0.92922)	0.1605 (0.24577)	0.1272 (1.24060)	-0.0066 (0.39159)	0.1448 (1.07915)	0.0817 (0.33119)	0.1138 (1.12868)	0.0992 (0.29430)
	Median	0.0699	0.0972	0.1880	0.0852	0.0000	0.0562	0.1781	0.0795	0.1353	0.0929
	Min, Max	-3.339, 2.279	-0.202, 0.784	-1.746, 2.049	-0.227, 0.958	-2.998, 3.474	-1.313, 0.675	-2.998, 3.474	-1.313, 0.958	-3.339, 3.474	-1.313, 0.958

- DB baseline: Baseline of confirmatory study.
- At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute statistical summaries.
- Percentile of height is calculated using "Trends in Average Height by Age" in "Physical Development and Health of Students (2017)" statistics by Ministry of Education. Culture, Sports, Science and Technology.
- z-score = (observed value - mean value of the reference population) / standard deviation value of reference population.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.4.3　12 誘導心電図検査

検証試験及び長期試験のいずれでも、心電図パラメータのうち PR 間隔、QRS 幅、QTcB 及び QTcF では治験依頼者が設定した基準を超える値を顕著な異常値とした。また、心電図総括評価責任者が QTc 延長に対する影響を総合的に評価した（2.7.4.1.1.2.4 項参照）。

(1) 検証試験

心電図パラメータ（心拍数、RR 間隔、PR 間隔、QRS 幅、QTcB 及び QTcF）のうち、QTcF 及び RR 間隔はプラセボ群と比べて 8 mg/日群及び 16 mg/日群で変動が大きかった。QTcF 平均値のベースラインは、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）で 385.89 msec、390.54 msec 及び 379.24 msec、最終評価時の平均変化量は 0.40 msec、1.18 msec 及び 5.67 msec であった。RR 間隔平均値のベースラインは 875.8 msec、876.3 msec 及び 867.1 msec、最終評価時の平均変化量は−8.6 msec、71.6 msec 及び 68.1 msec であった。顕著な PR 間隔延長（16 歳未満：180 msec 超、16 歳以上：200 msec 超）がプラセボ群、8 mg/日群及び 16 mg/日群で 3 名、1 名及び 1 名、顕著な QRS 幅延長（16 歳未満：110 msec 超、16 歳以上：120 msec 超）が 0 名、0 名及び 2 名にみられた（5.3.5.1.01 参照）。

QT 延長評価として QTcB 及び QTcF の顕著な異常値を示した被験者の割合を表 2.7.4.4-6 に示す。顕著な QTcB 高値（投与後に 460 msec 超）がプラセボ群、8 mg/日群及び 16 mg/日群で 2.1%（1/47 名）、8.0%（4/51 名）及び 1.9%（1/53 名）、顕著な QTcB 延長（ベースラインから 60 msec 以上延長）が 2.1%（1/47 名）、0%及び 1.9%（1/53 名）、顕著な QTcF 高値（投与後に 460 msec 超）が 0%、2.0%（1/51 名）及び 0%、顕著な QTcF 延長（ベースラインから 60 msec 以上延長）が 2.1%（1/47 名）、0%及び 1.9%（1/53 名）であった。

心電図総括評価責任者は以下の考察により、DSP-5423 が QT 間隔を延長する作用を有しているとは言えないと判断した。

- 群ごとの要約統計量では、8 mg/日群で QTcB 及び QTcF とそのベースラインからの変化量にプラセボ群と差はなく、16 mg/日群では QTcB とそのベースラインからの変化量にプラセボ群との差はなかった。
- 16 mg/日群では最終評価時の QTcF のベースラインからの変化量（Mean）が 5.67 msec と 5 msec を少し超える延長が認められたものの、外れ値である 2 名の被験者のベースラインからの変化量が平均値に影響を与えていること（この 2 名の変化量は個別に評価し臨床的に問題ないと判断した）、16 mg/日群での最終評価時の QTcF のベースラインからの変化量（Median）は 3.80 msec であることから、自然変動の範囲内の所見と判断でき、臨床的に問題ないと判断した。
- QTcB 及び QTcF が 450 msec、460 msec、480 msec、500 msec を超えた被験者数、QTcB 及び QTcF のベースラインからの変化量が 30 msec 及び 60 msec を超えて延長した被験者数は、8 mg/日群及び 16 mg/日群のいずれでもプラセボ群と差がなかった。

表 2.7.4.4-6　QT 延長評価（検証試験）

Safety Analysis Set

Criteria Visit	PLCB N = 47 n/m (%)	8 MG N = 51 n/m (%)	16 MG N = 53 n/m (%)	Active N = 104 n/m (%)
QTcB > 460 msec				
Baseline	1/47 (2.1%)	1/51 (2.0%)	0/53	1/104 (1.0%)
Any Post Baseline	1/47 (2.1%)	4/50 (8.0%)	1/53 (1.9%)	5/103 (4.9%)
QTcB >= 60 msec increased from baseline	1/47 (2.1%)	0/50	1/53 (1.9%)	1/103 (1.0%)
QTcF > 460 msec				
Baseline	0/47	0/51	0/53	0/104
Any Post Baseline	0/47	1/50 (2.0%)	0/53	1/103 (1.0%)
QTcF >= 60 msec increased from baseline	1/47 (2.1%)	0/50	1/53 (1.9%)	1/103 (1.0%)

- Measurement by Lead II is summarized.
- Any post baseline: subjects meeting the specified criteria at least once post-baseline observation.
- m is the total number of subjects with the corresponding visit values available.
- n and % are respectively the number and percentage of subjects meeting the specified criteria at the corresponding visit.
- QTcB is the QT interval corrected for heart rate using the Bazett's formula.
- QTcF is the QT interval corrected for heart rate using the Fridericia's formula.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

いずれの心電図パラメータも DB ベースラインに比べて投与後に臨床的に問題となる変動はなかった。なお、心電図パラメータで顕著な PR 間隔延長が 2 名、顕著な QRS 幅延長が 2 名にみられた（5.3.5.2.01 参照）。

QT 延長評価として、QTcB 及び QTcF の顕著な異常値を示した被験者の割合を表 2.7.4.4-7 に示す。Overall（104 名）のうち、顕著な QTcB 高値（投与後に 460 msec 超）が 3.8%（4 名）、顕著な QTcB 延長（ベースラインから 60 msec 以上延長）が 2.9%（3 名）、顕著な QTcF 高値（投与後に 460 msec 超）が 1.9%（2 名）、顕著な QTcF 延長（ベースラインから 60 msec 以上延長）が 1.0%（1 名）であった。

心電図総括評価責任者は以下の考察により、DSP-5423 が QT 間隔を延長する作用を有しているとは言えないと判断した。

- QTcB 及び QTcF とそのベースラインからの変化量（要約統計量）に問題となる異常変動は認められなかった。
- 各被験者の異常所見は、臨床的に問題となる変化ではないと判断した。

また、心電図総括評価責任者は、有害事象として QT 延長が報告された 1 名の心電図パラメータに異常所見はなく、QT 延長には該当しないと判断した。

表 2.7.4.4-7　QT 延長評価（長期試験）

Safety Analysis Set

Criteria Visit	DB-PLCB N = 36 n/m (%)	DB-8MG N = 37 n/m (%)	DB-16MG N = 33 n/m (%)	DB-Active N = 70 n/m (%)	Overall N = 106 n/m (%)
QTcB > 460 msec					
DB baseline	0/36	0/37	0/33	0/70	0/106
Any Post Baseline	1/36 (2.8%)	3/37 (8.1%)	0/31	3/68 (4.4%)	4/104 (3.8%)
QTcB >= 60 msec increased from baseline	0/36	0/37	3/31 (9.7%)	3/68 (4.4%)	3/104 (2.9%)
QTcF > 460 msec					
DB baseline	0/36	0/37	0/33	0/70	0/106
Any Post Baseline	0/36	2/37 (5.4%)	0/31	2/68 (2.9%)	2/104 (1.9%)
QTcF >= 60 msec increased from baseline	0/36	0/37	1/31 (3.2%)	1/68 (1.5%)	1/104 (1.0%)

- Measurement by Lead II is summarized.
- baseline: Baseline of confirmatory study.
- Any post baseline: subjects meeting the specified criteria at least once post-baseline observation.
- m is the total number of subjects with the corresponding visit values available.
- n and % are respectively the number and percentage of subjects meeting the specified criteria at the corresponding visit.
- QTcB is the QT interval corrected for heart rate using the Bazett's formula.
- QTcF is the QT interval corrected for heart rate using the Fridericia's formula.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.4.4　DIEPSS

(1) 検証試験

DIEPSS 合計スコア（概括重症度を除く）及び変化量を表 2.7.4.4-8 に示す。DIEPSS 合計スコア［Mean（SD）］のベースラインは、プラセボ群、8 mg/日群及び 16 mg/日群（以下同順）に 0.47（1.300）、0.71（2.773）及び 0.56（1.662）で、6 週時 LOCF の DIEPSS 合計スコア変化量［Mean（SD）］は−0.04（0.833）、0.08（1.560）及び 0.67（2.324）であった。16 mg/日群ではプラセボ群より合計スコア変化量が大きかった。

表 2.7.4.4-8　DIEPSS 合計スコア（概括重症度を除く）変化量（検証試験、治療期）

Safety Analysis Set

	PLCB N = 47		8 MG N = 51		16 MG N = 53		Active N = 104	
Visit	Observed	Change	Observed	Change	Observed	Change	Observed	Change
Baseline								
n	47		51		52		103	
Mean (SD)	0.47 (1.300)		0.71 (2.773)		0.56 (1.662)		0.63 (2.271)	
Median	0.00		0.00		0.00		0.00	
Min, Max	0, 6		0, 18		0, 9		0, 18	

Visit	PLCB N = 47 Observed	Change	8 MG N = 51 Observed	Change	16 MG N = 53 Observed	Change	Active N = 104 Observed	Change
Week 6 (LOCF)								
n	47	47	51	51	52	52	103	103
Mean (SD)	0.43 (1.347)	-0.04 (0.833)	0.78 (2.043)	0.08 (1.560)	1.23 (2.518)	0.67 (2.324)	1.01 (2.294)	0.38 (1.996)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 6	-3, 3	0, 12	-6, 6	0, 14	-2, 14	0, 14	-6, 14

- Week 6 (LOCF) endpoint is the last post-baseline observation in the treatment phase up to 7 days after final date of the study drug, except for transition phase.
- At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute statistical summaries.
- DIEPSS total score: Sum of 8 item scores not including overall severity.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

DIEPSS 合計スコア（概括重症度を除く）及び変化量を表 2.7.4.4-9 に示す。DIEPSS 合計スコア［Mean (SD)］の DB ベースラインは 0.24 (0.962) で、最終評価時 (LOCF) の DIEPSS 合計スコア変化量［Mean (SD)］は 0.08 (1.261) であった。

表 2.7.4.4-9　DIEPSS 合計スコア（概括重症度を除く）変化量（長期試験）

Safety Analysis Set

	DB-PLCB N = 36		DB-8MG N = 37		DB-16MG N = 33		DB-Active N = 70		Overall N = 106	
Visit	Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change
DB baseline										
n	36		37		33		70		106	
Mean (SD)	0.19 (0.822)		0.30 (1.309)		0.21 (0.600)		0.26 (1.031)		0.24 (0.962)	
Median	0.00		0.00		0.00		0.00		0.00	
Min, Max	0, 4		0, 7		0, 2		0, 7		0, 7	
Week 4										
n	36	36	35	35	31	31	66	66	102	102
Mean (SD)	0.19 (0.467)	0.00 (0.717)	0.20 (0.584)	0.00 (1.350)	0.19 (0.402)	-0.03 (0.795)	0.20 (0.503)	-0.02 (1.116)	0.20 (0.488)	-0.01 (0.990)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 2	-3, 1	0, 3	-7, 3	0, 1	-2, 1	0, 3	-7, 3	0, 3	-7, 3
Week 8										
n	34	34	35	35	31	31	66	66	100	100
Mean (SD)	0.41 (1.131)	0.21 (1.473)	0.26 (1.039)	0.06 (1.608)	0.26 (0.445)	0.03 (0.657)	0.26 (0.810)	0.05 (1.246)	0.31 (0.929)	0.10 (1.322)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 6	-4, 6	0, 6	-7, 6	0, 1	-2, 1	0, 6	-7, 6	0, 6	-7, 6
Week 12										
n	33	33	32	32	30	30	62	62	95	95
Mean (SD)	0.15 (0.364)	-0.06 (0.864)	0.25 (0.762)	0.03 (1.492)	0.33 (0.547)	0.10 (0.803)	0.29 (0.663)	0.06 (1.199)	0.24 (0.578)	0.02 (1.091)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 1	-4, 1	0, 3	-7, 3	0, 2	-2, 2	0, 3	-7, 3	0, 3	-7, 3

	DB-PLCB N = 36		DB-8MG N = 37		DB-16MG N = 33		DB-Active N = 70		Overall N = 106	
Visit	Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change
Week 24										
n	30	30	29	29	25	25	54	54	84	84
Mean (SD)	0.33 (1.061)	0.10 (0.481)	0.28 (0.702)	0.03 (1.523)	0.24 (0.597)	0.08 (0.759)	0.26 (0.650)	0.06 (1.220)	0.29 (0.815)	0.07 (1.015)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 5	-1, 2	0, 3	-7, 3	0, 2	-2, 2	0, 3	-7, 3	0, 5	-7, 3
Week 36										
n	26	26	26	26	21	21	47	47	73	73
Mean (SD)	0.12 (0.431)	0.12 (0.431)	0.15 (0.368)	-0.12 (1.451)	0.24 (0.539)	0.05 (0.865)	0.19 (0.449)	-0.04 (1.215)	0.16 (0.441)	0.01 (1.007)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 2	0, 2	0, 1	-7, 1	0, 2	-2, 2	0, 2	-7, 2	0, 2	-7, 2
Week 52										
n	22	22	23	23	18	18	41	41	63	63
Mean (SD)	0.00 (0.000)	0.00 (0.000)	0.57 (1.879)	0.57 (1.879)	0.28 (0.958)	0.28 (0.958)	0.44 (1.534)	0.44 (1.534)	0.29 (1.250)	0.29 (1.250)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 0	0, 0	0, 9	0, 9	0, 4	0, 4	0, 9	0, 9	0, 9	0, 9
LOCF endpoint										
n	36	36	37	37	32	32	69	69	105	105
Mean (SD)	0.22 (0.722)	0.03 (0.291)	0.49 (1.609)	0.19 (1.927)	0.22 (0.751)	0.00 (0.950)	0.36 (1.283)	0.10 (1.545)	0.31 (1.121)	0.08 (1.261)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min, Max	0, 3	-1, 1	0, 9	-7, 9	0, 4	-2, 4	0, 9	-7, 9	0, 9	-7, 9

	DB-PLCB N = 36		DB-8MG N = 37		DB-16MG N = 33		DB-Active N = 70		Overall N = 106	
Visit	Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change

- DB baseline: Baseline of confirmatory study.
- At each post-baseline visit, only data from subjects with both baseline and the corresponding visit values available were used to compute statistical summaries.
- DIEPSS total score: Sum of 8 item scores not including overall severity.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.4.5 CGI-SS

CGI-SS の悪化率を、状態変化スコアで 6（Much worse）又は 7（Very much worse）になった被験者の割合と定義した（2.7.4.1.1.2.6 項参照）。

(1) 検証試験

CGI-SS の悪化率を表 2.7.4.4-10 に示す。6 週時までのうち最も高い CGI-SS スコアに基づく CGI-SS の悪化率は、プラセボ群、8 mg/日群及び 16 mg/日群で 4.3%、0%及び 1.9%であり、自殺リスクの明らかな悪化はみられなかった。

表 2.7.4.4-10　CGI-SS の悪化率（検証試験）

Safety Analysis Set

Visit	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Worsening				
Week 1	n = 47	n = 51	n = 52	n = 103
Yes	0	0	1 (1.9%)	1 (1.0%)
No	47 (100.0%)	51 (100.0%)	51 (98.1%)	102 (99.0%)
Week 2	n = 46	n = 47	n = 50	n = 97
Yes	1 (2.2%)	0	0	0
No	45 (97.8%)	47 (100.0%)	50 (100.0%)	97 (100.0%)
Week 4	n = 44	n = 45	n = 47	n = 92
Yes	1 (2.3%)	0	0	0
No	43 (97.7%)	45 (100.0%)	47 (100.0%)	92 (100.0%)
Week 6	n = 41	n = 39	n = 39	n = 78
Yes	1 (2.4%)	0	0	0
No	40 (97.6%)	39 (100.0%)	39 (100.0%)	78 (100.0%)
Week 6 (LOCF)	n = 47	n = 51	n = 52	n = 103
Yes	2 (4.3%)	0	1 (1.9%)	1 (1.0%)
No	45 (95.7%)	51 (100.0%)	51 (98.1%)	102 (99.0%)
Worst value	n = 47	n = 51	n = 52	n = 103
Yes	2 (4.3%)	0	1 (1.9%)	1 (1.0%)
No	45 (95.7%)	51 (100.0%)	51 (98.1%)	102 (99.0%)

- Week 6 (LOCF) endpoint is the last post-baseline observation in the treatment phase up to 7 days after final date of the study drug, except for transition phase.
- Worst value: the worst post-baseline observation in the treatment phase up to 7 days after final date of the study drug, except for transition phase.
- CGI-SS worsened is defined as "much worse" or "very much worse" in 2nd item "How much the patient's suicidality changed compared with condition at baseline" (CGI-SS 2nd item score of 6 or 7).
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

CGI-SS の悪化率を表 2.7.4.4-11 に示す。52 週時までのうち最も高い CGI-SS スコアに基づく CGI-SS の悪化率は Overall で 3.8%であり、自殺リスクの明らかな悪化はみられなかった。

表 2.7.4.4-11　CGI-SS の悪化率（長期試験）

Safety Analysis Set

Visit	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Worsening					
Week 4	n = 36	n = 35	n = 31	n = 66	n = 102
Yes	1 (2.8%)	0	0	0	1 (1.0%)
No	35 (97.2%)	35 (100.0%)	31 (100.0%)	66 (100.0%)	101 (99.0%)
Week 8	n = 34	n = 35	n = 31	n = 66	n = 100
Yes	0	0	0	0	0
No	34 (100.0%)	35 (100.0%)	31 (100.0%)	66 (100.0%)	100 (100.0%)
Week 12	n = 33	n = 32	n = 30	n = 62	n = 95
Yes	1 (3.0%)	0	0	0	1 (1.1%)
No	32 (97.0%)	32 (100.0%)	30 (100.0%)	62 (100.0%)	94 (98.9%)
Week 24	n = 30	n = 29	n = 25	n = 54	n = 84
Yes	0	0	0	0	0
No	30 (100.0%)	29 (100.0%)	25 (100.0%)	54 (100.0%)	84 (100.0%)
Week 36	n = 26	n = 26	n = 21	n = 47	n = 73
Yes	0	0	0	0	0
No	26 (100.0%)	26 (100.0%)	21 (100.0%)	47 (100.0%)	73 (100.0%)
Week 52	n = 22	n = 23	n = 18	n = 41	n = 63
Yes	0	0	0	0	0
No	22 (100.0%)	23 (100.0%)	18 (100.0%)	41 (100.0%)	63 (100.0%)
LOCF endpoint	n = 36	n = 37	n = 31	n = 68	n = 104
Yes	2 (5.6%)	0	0	0	2 (1.9%)
No	34 (94.4%)	37 (100.0%)	31 (100.0%)	68 (100.0%)	102 (98.1%)
Worst value	n = 36	n = 37	n = 31	n = 68	n = 104
Yes	2 (5.6%)	2 (5.4%)	0	2 (2.9%)	4 (3.8%)
No	34 (94.4%)	35 (94.6%)	31 (100.0%)	66 (97.1%)	100 (96.2%)

Visit	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106

- CGI-SS worsened is defined as "much worse" or "very much worse" in 2nd item "How much the patient's suicidality changed compared with condition at baseline" (CGI-SS 2nd item score of 6 or 7).
- Worst value: the worst post-baseline observation.
- n is number of subjects who evaluated at the visit.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.4.6　抗パーキンソン薬の併用割合

(1) 検証試験

抗パーキンソン薬の併用割合を表 2.7.4.4-12 に示す。治験薬投与前に抗パーキンソン薬を併用した被験者数は8 mg/日群の1名のみで、治療期での併用割合はプラセボ群で4.3%、8 mg/日群で 25.5%、16 mg/日群で 37.7%と、プラセボ群、8 mg/日群、16 mg/日群の順に高くなった。

表 2.7.4.4-12　抗パーキンソン薬の併用割合（検証試験）

Safety Analysis Set

Visit	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Prior	n = 47	n = 51	n = 53	n = 104
Use	0	1 (2.0%)	0	1 (1.0%)
Not use	47 (100.0%)	50 (98.0%)	53 (100.0%)	103 (99.0%)
Day 1 to 7	n = 47	n = 51	n = 53	n = 104
Use	1 (2.1%)	2 (3.9%)	1 (1.9%)	3 (2.9%)
Not use	46 (97.9%)	49 (96.1%)	52 (98.1%)	101 (97.1%)
Day 8 to 14	n = 46	n = 49	n = 50	n = 99
Use	2 (4.3%)	7 (14.3%)	2 (4.0%)	9 (9.1%)
Not use	44 (95.7%)	42 (85.7%)	48 (96.0%)	90 (90.9%)
Day 15 to 28	n = 45	n = 46	n = 47	n = 93
Use	2 (4.4%)	12 (26.1%)	17 (36.2%)	29 (31.2%)
Not use	43 (95.6%)	34 (73.9%)	30 (63.8%)	64 (68.8%)
Day 29 to 42	n = 41	n = 39	n = 39	n = 78
Use	2 (4.9%)	9 (23.1%)	18 (46.2%)	27 (34.6%)
Not use	39 (95.1%)	30 (76.9%)	21 (53.8%)	51 (65.4%)
Later than Day 42	n = 36	n = 38	n = 33	n = 71
Use	2 (5.6%)	9 (23.7%)	16 (48.5%)	25 (35.2%)
Not use	34 (94.4%)	29 (76.3%)	17 (51.5%)	46 (64.8%)

Visit	PLCB N = 47	8 MG N = 51	16 MG N = 53	Active N = 104
Any timepoint	n = 47	n = 51	n = 53	n = 104
Use	2 (4.3%)	13 (25.5%)	20 (37.7%)	33 (31.7%)
Not use	45 (95.7%)	38 (74.5%)	33 (62.3%)	71 (68.3%)

- If antiparkinson drugs is used at least once in any period after Day 1, it will be counted as "use" in "any timepoint", except for transition phase.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

抗パーキンソン薬の併用割合を表 2.7.4.4-13 に示す。長期試験の治験薬投与開始時に抗パーキンソン薬を使用していた被験者は 23.6%で、長期試験の治験薬投与開始後に 1 回でも抗パーキンソン薬を併用した被験者は 45.3%であった。

表 2.7.4.4-13　抗パーキンソン薬の併用割合（長期試験）

Safety Analysis Set

	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Prior	n = 36	n = 37	n = 33	n = 70	n = 106
Use	2 (5.6%)	9 (24.3%)	14 (42.4%)	23 (32.9%)	25 (23.6%)
Not use	34 (94.4%)	28 (75.7%)	19 (57.6%)	47 (67.1%)	81 (76.4%)
Day 1 to 7	n = 36	n = 37	n = 33	n = 70	n = 106
Use	2 (5.6%)	9 (24.3%)	15 (45.5%)	24 (34.3%)	26 (24.5%)
Not use	34 (94.4%)	28 (75.7%)	18 (54.5%)	46 (65.7%)	80 (75.5%)
Day 8 to 14	n = 36	n = 36	n = 33	n = 69	n = 105
Use	3 (8.3%)	10 (27.8%)	15 (45.5%)	25 (36.2%)	28 (26.7%)
Not use	33 (91.7%)	26 (72.2%)	18 (54.5%)	44 (63.8%)	77 (73.3%)
Day 15 to 28	n = 36	n = 35	n = 32	n = 67	n = 103
Use	3 (8.3%)	10 (28.6%)	15 (46.9%)	25 (37.3%)	28 (27.2%)
Not use	33 (91.7%)	25 (71.4%)	17 (53.1%)	42 (62.7%)	75 (72.8%)
Day 29 to 56	n = 34	n = 35	n = 32	n = 67	n = 101
Use	6 (17.6%)	11 (31.4%)	16 (50.0%)	27 (40.3%)	33 (32.7%)
Not use	28 (82.4%)	24 (68.6%)	16 (50.0%)	40 (59.7%)	68 (67.3%)
Day 57 to 84	n = 34	n = 34	n = 30	n = 64	n = 98
Use	9 (26.5%)	11 (32.4%)	13 (43.3%)	24 (37.5%)	33 (33.7%)
Not use	25 (73.5%)	23 (67.6%)	17 (56.7%)	40 (62.5%)	65 (66.3%)
Day 85 to 112	n = 32	n = 31	n = 28	n = 59	n = 91

	DB-PLCB N = 36	DB-8MG N = 37	DB-16MG N = 33	DB-Active N = 70	Overall N = 106
Use	9 (28.1%)	10 (32.3%)	11 (39.3%)	21 (35.6%)	30 (33.0%)
Not use	23 (71.9%)	21 (67.7%)	17 (60.7%)	38 (64.4%)	61 (67.0%)
Day 113 to 140	n = 31	n = 30	n = 27	n = 57	n = 88
Use	7 (22.6%)	9 (30.0%)	11 (40.7%)	20 (35.1%)	27 (30.7%)
Not use	24 (77.4%)	21 (70.0%)	16 (59.3%)	37 (64.9%)	61 (69.3%)
Day 141 to 168	n = 30	n = 29	n = 27	n = 56	n = 86
Use	9 (30.0%)	9 (31.0%)	9 (33.3%)	18 (32.1%)	27 (31.4%)
Not use	21 (70.0%)	20 (69.0%)	18 (66.7%)	38 (67.9%)	59 (68.6%)
Day 169 to 196	n = 27	n = 28	n = 25	n = 53	n = 80
Use	8 (29.6%)	11 (39.3%)	8 (32.0%)	19 (35.8%)	27 (33.8%)
Not use	19 (70.4%)	17 (60.7%)	17 (68.0%)	34 (64.2%)	53 (66.3%)
Day 197 to 252	n = 26	n = 28	n = 24	n = 52	n = 78
Use	8 (30.8%)	10 (35.7%)	8 (33.3%)	18 (34.6%)	26 (33.3%)
Not use	18 (69.2%)	18 (64.3%)	16 (66.7%)	34 (65.4%)	52 (66.7%)
Day 253 to 308	n = 23	n = 25	n = 20	n = 45	n = 68
Use	7 (30.4%)	9 (36.0%)	5 (25.0%)	14 (31.1%)	21 (30.9%)
Not use	16 (69.6%)	16 (64.0%)	15 (75.0%)	31 (68.9%)	47 (69.1%)
Day 309 to 364	n = 22	n = 24	n = 20	n = 44	n = 66
Use	9 (40.9%)	9 (37.5%)	5 (25.0%)	14 (31.8%)	23 (34.8%)
Not use	13 (59.1%)	15 (62.5%)	15 (75.0%)	30 (68.2%)	43 (65.2%)
Day 365 or after	n = 16	n = 21	n = 9	n = 30	n = 46
Use	6 (37.5%)	6 (28.6%)	2 (22.2%)	8 (26.7%)	14 (30.4%)
Not use	10 (62.5%)	15 (71.4%)	7 (77.8%)	22 (73.3%)	32 (69.6%)
Any timepoint	n = 36	n = 37	n = 33	n = 70	n = 106
Use	14 (38.9%)	16 (43.2%)	18 (54.5%)	34 (48.6%)	48 (45.3%)
Not use	22 (61.1%)	21 (56.8%)	15 (45.5%)	36 (51.4%)	58 (54.7%)

- "Prior" antiparkinson drugs are defined as antiparkinson drugs with start dates before the date of start of study drug of extension study.
- If antiparkinson drugs is used at least once in any period after Day 1, it will be counted as "use" in "any timepoint".
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

2.7.4.5 特別な患者集団及び状況下における安全性

2.7.4.5.1 内因性要因

(1) 検証試験

年齢（15 歳未満、15 歳以上）別、性別、体重（50 kg 未満、50 kg 以上）別及び発症回数（1 回、2 回以上）別有害事象及び副作用の発現状況を表 2.7.4.5-1～表 2.7.4.5-4 に示す。年齢、性別、体重、発症回数別で、有害事象、重篤な有害事象、投与中止に至った有害事象、錐体外路症状関連有害事象、発育障害関連有害事象及びそれらの副作用の発現状況に、特に大きな違いがある部分集団はみられなかった。

プロラクチン増加関連有害事象は、体重 50 kg 未満の集団ではプラセボ群、8 mg/日群及び 16 mg/日群（以下同順）でそれぞれ 0%（0/17 名）、29.4%（5/17 名）及び 43.8%（7/16 名）に発現し、体重 50 kg 以上の集団ではそれぞれ 6.7%（2/30 名）、8.8%（3/34 名）及び 27.8%（10/36 名）に発現した。体重の大小にかかわらず有害事象の発現割合はプラセボ群と比べて 8 mg/日群及び 16 mg/日群で高い傾向がみられ、8 mg/日群及び 16 mg/日群のいずれの群でも体重 50 kg 未満の集団の方が 50 kg 以上の集団より発現割合が高かった。また、プロラクチン増加関連有害事象は、初発の集団ではそれぞれ 5.3%（2/38 名）、19.0%（8/42 名）及び 44.4%（16/36 名）に発現し、発症 2 回目以上の集団ではそれぞれ 0%（0/7 名）、0%（0/8 名）及び 6.3%（1/16 名）に発現した。発症回数にかかわらず有害事象の発現割合はプラセボ群と比べて 16 mg/日群で高い傾向がみられ、各群を集団間で比べるといずれの群でも初発の集団の方が発症 2 回目以上の集団より発現割合が高かった。

表 2.7.4.5-1　年齢（15 歳未満、15 歳以上）別有害事象及び副作用の発現状況（検証試験、治療期）

Safety Analysis Set
Age < 15 years, N = 46

	PLCB N = 14			8 MG N = 16			16 MG N = 16			Active N = 32		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	11	(78.6%)	38	13	(81.3%)	53	15	(93.8%)	54	28	(87.5%)	107
Death	0			0			0			0		
Leading to discontinuation	0			2	(12.5%)	2	2	(12.5%)	3	4	(12.5%)	5
Serious	0			1	(6.3%)	1	0			1	(3.1%)	1
Extrapyramidal syndrome	0			4	(25.0%)	5	9	(56.3%)	25	13	(40.6%)	30
Prolactin related AE	1	(7.1%)	1	3	(18.8%)	6	8	(50.0%)	12	11	(34.4%)	18
Failure to thrive	0			0			0			0		
Subject with AE related to study drug	2	(14.3%)	10	9	(56.3%)	25	13	(81.3%)	41	22	(68.8%)	66
Death	0			0			0			0		
Leading to discontinuation	0			2	(12.5%)	2	2	(12.5%)	3	4	(12.5%)	5
Serious	0			1	(6.3%)	1	0			1	(3.1%)	1
Extrapyramidal syndrome	0			4	(25.0%)	5	9	(56.3%)	25	13	(40.6%)	30
Prolactin related AE	1	(7.1%)	1	3	(18.8%)	6	8	(50.0%)	12	11	(34.4%)	18
Failure to thrive	0			0			0			0		

Age >= 15 years, N = 105

	PLCB N = 33			8 MG N = 35			16 MG N = 37			Active N = 72		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	21	(63.6%)	53	28	(80.0%)	108	34	(91.9%)	160	62	(86.1%)	268
Death	0			0			0			0		
Leading to discontinuation	3	(9.1%)	4	3	(8.6%)	3	4	(10.8%)	5	7	(9.7%)	8
Serious	1	(3.0%)	1	0			0			0		
Extrapyramidal syndrome	2	(6.1%)	3	9	(25.7%)	20	18	(48.6%)	37	27	(37.5%)	57
Prolactin related AE	1	(3.0%)	1	5	(14.3%)	9	9	(24.3%)	13	14	(19.4%)	22
Failure to thrive	1	(3.0%)	1	2	(5.7%)	3	0			2	(2.8%)	3
Subject with AE related to study drug	10	(30.3%)	18	19	(54.3%)	59	27	(73.0%)	87	46	(63.9%)	146
Death	0			0			0			0		
Leading to discontinuation	3	(9.1%)	4	2	(5.7%)	2	3	(8.1%)	4	5	(6.9%)	6
Serious	1	(3.0%)	1	0			0			0		
Extrapyramidal syndrome	2	(6.1%)	3	9	(25.7%)	20	17	(45.9%)	36	26	(36.1%)	56
Prolactin related AE	1	(3.0%)	1	5	(14.3%)	9	9	(24.3%)	13	14	(19.4%)	22
Failure to thrive	1	(3.0%)	1	2	(5.7%)	3	0			2	(2.8%)	3

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.5-2　性別有害事象及び副作用の発現状況（検証試験、治療期）

Safety Analysis Set
Female, N = 87

	PLCB N = 27			8 MG N = 30			16 MG N = 30			Active N = 60		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	18	(66.7%)	53	23	(76.7%)	80	29	(96.7%)	136	52	(86.7%)	216
Death	0			0			0			0		
Leading to discontinuation	1	(3.7%)	2	2	(6.7%)	2	2	(6.7%)	3	4	(6.7%)	5
Serious	0			0			0			0		
Extrapyramidal syndrome	2	(7.4%)	3	7	(23.3%)	15	18	(60.0%)	45	25	(41.7%)	60
Prolactin related AE	2	(7.4%)	2	4	(13.3%)	7	10	(33.3%)	15	14	(23.3%)	22
Failure to thrive	0			0			0			0		
Subject with AE related to study drug	6	(22.2%)	12	14	(46.7%)	39	25	(83.3%)	77	39	(65.0%)	116
Death	0			0			0			0		
Leading to discontinuation	1	(3.7%)	2	2	(6.7%)	2	1	(3.3%)	2	3	(5.0%)	4
Serious	0			0			0			0		
Extrapyramidal syndrome	2	(7.4%)	3	7	(23.3%)	15	17	(56.7%)	44	24	(40.0%)	59
Prolactin related AE	2	(7.4%)	2	4	(13.3%)	7	10	(33.3%)	15	14	(23.3%)	22
Failure to thrive	0			0			0			0		

Male, N = 64

	PLCB N = 20			8 MG N = 21			16 MG N = 23			Active N = 44		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	14	(70.0%)	38	18	(85.7%)	81	20	(87.0%)	78	38	(86.4%)	159
Death	0			0			0			0		
Leading to discontinuation	2	(10.0%)	2	3	(14.3%)	3	4	(17.4%)	5	7	(15.9%)	8
Serious	1	(5.0%)	1	1	(4.8%)	1	0			1	(2.3%)	1
Extrapyramidal syndrome	0			6	(28.6%)	10	9	(39.1%)	17	15	(34.1%)	27
Prolactin related AE	0			4	(19.0%)	8	7	(30.4%)	10	11	(25.0%)	18
Failure to thrive	1	(5.0%)	1	2	(9.5%)	3	0			2	(4.5%)	3
Subject with AE related to study drug	6	(30.0%)	16	14	(66.7%)	45	15	(65.2%)	51	29	(65.9%)	96
Death	0			0			0			0		
Leading to discontinuation	2	(10.0%)	2	2	(9.5%)	2	4	(17.4%)	5	6	(13.6%)	7
Serious	1	(5.0%)	1	1	(4.8%)	1	0			1	(2.3%)	1
Extrapyramidal syndrome	0			6	(28.6%)	10	9	(39.1%)	17	15	(34.1%)	27
Prolactin related AE	0			4	(19.0%)	8	7	(30.4%)	10	11	(25.0%)	18
Failure to thrive	1	(5.0%)	1	2	(9.5%)	3	0			2	(4.5%)	3

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.5-3　体重（50 kg 未満、50 kg 以上）別有害事象及び副作用の発現状況（検証試験、治療期）

Safety Analysis Set
Weight < 50 kg, N = 50

	PLCB N = 17			8 MG N = 17			16 MG N = 16			Active N = 33		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	10	(58.8%)	31	16	(94.1%)	65	15	(93.8%)	50	31	(93.9%)	115
Death	0			0			0			0		
Leading to discontinuation	1	(5.9%)	2	4	(23.5%)	4	3	(18.8%)	4	7	(21.2%)	8
Serious	0			1	(5.9%)	1	0			1	(3.0%)	1
Extrapyramidal syndrome	1	(5.9%)	1	6	(35.3%)	12	11	(68.8%)	23	17	(51.5%)	35
Prolactin related AE	0			5	(29.4%)	9	7	(43.8%)	10	12	(36.4%)	19
Failure to thrive	0			0			0			0		
Subject with AE related to study drug	5	(29.4%)	12	14	(82.4%)	36	14	(87.5%)	43	28	(84.8%)	79
Death	0			0			0			0		
Leading to discontinuation	1	(5.9%)	2	3	(17.6%)	3	2	(12.5%)	3	5	(15.2%)	6
Serious	0			1	(5.9%)	1	0			1	(3.0%)	1
Extrapyramidal syndrome	1	(5.9%)	1	6	(35.3%)	12	11	(68.8%)	23	17	(51.5%)	35
Prolactin related AE	0			5	(29.4%)	9	7	(43.8%)	10	12	(36.4%)	19
Failure to thrive	0			0			0			0		

Weight >= 50 kg, N = 100

	PLCB N = 30			8 MG N = 34			16 MG N = 36			Active N = 70		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	22	(73.3%)	60	25	(73.5%)	96	34	(94.4%)	164	59	(84.3%)	260
Death	0			0			0			0		
Leading to discontinuation	2	(6.7%)	2	1	(2.9%)	1	3	(8.3%)	4	4	(5.7%)	5
Serious	1	(3.3%)	1	0			0			0		
Extrapyramidal syndrome	1	(3.3%)	2	7	(20.6%)	13	16	(44.4%)	39	23	(32.9%)	52
Prolactin related AE	2	(6.7%)	2	3	(8.8%)	6	10	(27.8%)	15	13	(18.6%)	21
Failure to thrive	1	(3.3%)	1	2	(5.9%)	3	0			2	(2.9%)	3
Subject with AE related to study drug	7	(23.3%)	16	14	(41.2%)	48	26	(72.2%)	85	40	(57.1%)	133
Death	0			0			0			0		
Leading to discontinuation	2	(6.7%)	2	1	(2.9%)	1	3	(8.3%)	4	4	(5.7%)	5
Serious	1	(3.3%)	1	0			0			0		
Extrapyramidal syndrome	1	(3.3%)	2	7	(20.6%)	13	15	(41.7%)	38	22	(31.4%)	51
Prolactin related AE	2	(6.7%)	2	3	(8.8%)	6	10	(27.8%)	15	13	(18.6%)	21
Failure to thrive	1	(3.3%)	1	2	(5.9%)	3	0			2	(2.9%)	3

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

表 2.7.4.5-4　発症回数（1 回、2 回以上）別有害事象及び副作用の発現状況（検証試験、治療期）

Safety Analysis Set
Number of Episodes = 1, N = 116

	PLCB N = 38			8 MG N = 42			16 MG N = 36			Active N = 78		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	25	(65.8%)	72	34	(81.0%)	134	33	(91.7%)	163	67	(85.9%)	297
Death	0			0			0			0		
Leading to discontinuation	2	(5.3%)	3	5	(11.9%)	5	4	(11.1%)	5	9	(11.5%)	10
Serious	1	(2.6%)	1	1	(2.4%)	1	0			1	(1.3%)	1
Extrapyramidal syndrome	2	(5.3%)	3	10	(23.8%)	18	18	(50.0%)	44	28	(35.9%)	62
Prolactin related AE	2	(5.3%)	2	8	(19.0%)	15	16	(44.4%)	23	24	(30.8%)	38
Failure to thrive	1	(2.6%)	1	2	(4.8%)	3	0			2	(2.6%)	3
Subject with AE related to study drug	10	(26.3%)	26	24	(57.1%)	76	27	(75.0%)	93	51	(65.4%)	169
Death	0			0			0			0		
Leading to discontinuation	2	(5.3%)	3	4	(9.5%)	4	3	(8.3%)	4	7	(9.0%)	8
Serious	1	(2.6%)	1	1	(2.4%)	1	0			1	(1.3%)	1
Extrapyramidal syndrome	2	(5.3%)	3	10	(23.8%)	18	17	(47.2%)	43	27	(34.6%)	61
Prolactin related AE	2	(5.3%)	2	8	(19.0%)	15	16	(44.4%)	23	24	(30.8%)	38
Failure to thrive	1	(2.6%)	1	2	(4.8%)	3	0			2	(2.6%)	3

Number of Episodes >= 2, N = 31

	PLCB N = 7			8 MG N = 8			16 MG N = 16			Active N = 24		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	6	(85.7%)	17	6	(75.0%)	21	16	(100.0%)	51	22	(91.7%)	72
Death	0			0			0			0		
Leading to discontinuation	1	(14.3%)	1	0			2	(12.5%)	3	2	(8.3%)	3
Serious	0			0			0			0		
Extrapyramidal syndrome	0			2	(25.0%)	5	9	(56.3%)	18	11	(45.8%)	23
Prolactin related AE	0			0			1	(6.3%)	2	1	(4.2%)	2
Failure to thrive	0			0			0			0		
Subject with AE related to study drug	2	(28.6%)	2	3	(37.5%)	6	13	(81.3%)	35	16	(66.7%)	41
Death	0			0			0			0		
Leading to discontinuation	1	(14.3%)	1	0			2	(12.5%)	3	2	(8.3%)	3
Serious	0			0			0			0		
Extrapyramidal syndrome	0			2	(25.0%)	5	9	(56.3%)	18	11	(45.8%)	23
Prolactin related AE	0			0			1	(6.3%)	2	1	(4.2%)	2
Failure to thrive	0			0			0			0		

- Abbreviations: AE, adverse event.
- Adverse events in treatment phase are defined as adverse events with a start date on or after the date of first dose through 1 day before the start date of transition phase or the end date of follow-up phase for the subjects who didn't start transition phase.
- Adverse events related to study drug are defined as adverse events reported as 'definite', 'probable', 'possible', 'unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group: PLCB = Placebo; 8 MG = DSP-5423 8 mg; 16 MG = DSP-5423 16 mg; Active = DSP-5423 8 mg or 16 mg.

(2) 長期試験

年齢（15 歳未満、15 歳以上）別、性別、体重（50 kg 未満、50 kg 以上）別及び発症回数（1 回、2 回以上）別有害事象及び副作用の発現状況を表 2.7.4.5-5～表 2.7.4.5-8 に示す。年齢、性別、体重、発症回数別で、有害事象、重篤な有害事象、投与中止に至った有害事象、錐体外路症状関連有害事象、プロラクチン増加関連有害事象、発育障害関連有害事象及びそれらの副作用の発現状況に、特に大きな違いがある部分集団はみられなかった。

表 2.7.4.5-5　年齢（15 歳未満、15 歳以上）別有害事象及び副作用の発現状況（長期試験）

Safety Analysis Set
Age < 15 years

	DB-PLCB N = 9			DB-8MG N = 11			DB-16MG N = 10			DB-Active N = 21			Overall N = 30		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	8	(88.9%)	78	10	(90.9%)	95	9	(90.0%)	55	19	(90.5%)	150	27	(90.0%)	228
Death	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Serious	0			2	(18.2%)	2	1	(10.0%)	1	3	(14.3%)	3	3	(10.0%)	3
Extrapyramidal syndrome	3	(33.3%)	4	5	(45.5%)	9	3	(30.0%)	3	8	(38.1%)	12	11	(36.7%)	16
Prolactin related AE	2	(22.2%)	2	5	(45.5%)	5	2	(20.0%)	3	7	(33.3%)	8	9	(30.0%)	10
Failure to thrive	2	(22.2%)	2	3	(27.3%)	3	2	(20.0%)	2	5	(23.8%)	5	7	(23.3%)	7
Subject with AE related to study drug	6	(66.7%)	14	7	(63.6%)	22	6	(60.0%)	17	13	(61.9%)	39	19	(63.3%)	53
Death	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Serious	0			0			0			0			0		
Extrapyramidal syndrome	3	(33.3%)	4	5	(45.5%)	9	2	(20.0%)	2	7	(33.3%)	11	10	(33.3%)	15
Prolactin related AE	1	(11.1%)	1	5	(45.5%)	5	2	(20.0%)	3	7	(33.3%)	8	8	(26.7%)	9
Failure to thrive	2	(22.2%)	2	1	(9.1%)	1	2	(20.0%)	2	3	(14.3%)	3	5	(16.7%)	5

Age >= 15 years

	DB-PLCB N = 27			DB-8MG N = 26			DB-16MG N = 23			DB-Active N = 49			Overall N = 76		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	25	(92.6%)	236	24	(92.3%)	139	20	(87.0%)	172	44	(89.8%)	311	69	(90.8%)	547
Death	0			0			2	(8.7%)	2	2	(4.1%)	2	2	(2.6%)	2
Leading to discontinuation	4	(14.8%)	4	3	(11.5%)	4	2	(8.7%)	2	5	(10.2%)	6	9	(11.8%)	10
Serious	8	(29.6%)	9	3	(11.5%)	3	3	(13.0%)	3	6	(12.2%)	6	14	(18.4%)	15
Extrapyramidal syndrome	14	(51.9%)	30	8	(30.8%)	15	8	(34.8%)	13	16	(32.7%)	28	30	(39.5%)	58
Prolactin related AE	7	(25.9%)	7	5	(19.2%)	5	3	(13.0%)	3	8	(16.3%)	8	15	(19.7%)	15
Failure to thrive	2	(7.4%)	3	4	(15.4%)	4	2	(8.7%)	2	6	(12.2%)	6	8	(10.5%)	9
Subject with AE related to study drug	18	(66.7%)	66	18	(69.2%)	43	14	(60.9%)	28	32	(65.3%)	71	50	(65.8%)	137
Death	0			0			0			0			0		
Leading to discontinuation	0			2	(7.7%)	2	0			2	(4.1%)	2	2	(2.6%)	2
Serious	0			1	(3.8%)	1	0			1	(2.0%)	1	1	(1.3%)	1
Extrapyramidal syndrome	14	(51.9%)	30	8	(30.8%)	15	7	(30.4%)	11	15	(30.6%)	26	29	(38.2%)	56
Prolactin related AE	7	(25.9%)	7	5	(19.2%)	5	3	(13.0%)	3	8	(16.3%)	8	15	(19.7%)	15
Failure to thrive	0			3	(11.5%)	3	2	(8.7%)	2	5	(10.2%)	5	5	(6.6%)	5

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.5-6　性別有害事象及び副作用の発現状況（長期試験）

Safety Analysis Set
Female

	DB-PLCB N = 22			DB-8MG N = 21			DB-16MG N = 18			DB-Active N = 39			Overall N = 61		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	21	(95.5%)	222	18	(85.7%)	152	17	(94.4%)	142	35	(89.7%)	294	56	(91.8%)	516
Death	0			0			1	(5.6%)	1	1	(2.6%)	1	1	(1.6%)	1
Leading to discontinuation	3	(13.6%)	3	1	(4.8%)	1	1	(5.6%)	1	2	(5.1%)	2	5	(8.2%)	5
Serious	7	(31.8%)	8	3	(14.3%)	3	3	(16.7%)	3	6	(15.4%)	6	13	(21.3%)	14
Extrapyramidal syndrome	11	(50.0%)	23	10	(47.6%)	19	8	(44.4%)	12	18	(46.2%)	31	29	(47.5%)	54
Prolactin related AE	4	(18.2%)	4	7	(33.3%)	7	4	(22.2%)	4	11	(28.2%)	11	15	(24.6%)	15
Failure to thrive	3	(13.6%)	4	5	(23.8%)	5	1	(5.6%)	1	6	(15.4%)	6	9	(14.8%)	10
Subject with AE related to study drug	16	(72.7%)	52	15	(71.4%)	46	13	(72.2%)	26	28	(71.8%)	72	44	(72.1%)	124
Death	0			0			0			0			0		
Leading to discontinuation	0			1	(4.8%)	1	0			1	(2.6%)	1	1	(1.6%)	1
Serious	0			0			0			0			0		
Extrapyramidal syndrome	11	(50.0%)	23	10	(47.6%)	19	6	(33.3%)	9	16	(41.0%)	28	27	(44.3%)	51
Prolactin related AE	3	(13.6%)	3	7	(33.3%)	7	4	(22.2%)	4	11	(28.2%)	11	14	(23.0%)	14
Failure to thrive	1	(4.5%)	1	3	(14.3%)	3	1	(5.6%)	1	4	(10.3%)	4	5	(8.2%)	5

Male

	DB-PLCB N = 14			DB-8MG N = 16			DB-16MG N = 15			DB-Active N = 31			Overall N = 45		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	12	(85.7%)	92	16	(100.0%)	82	12	(80.0%)	85	28	(90.3%)	167	40	(88.9%)	259
Death	0			0			1	(6.7%)	1	1	(3.2%)	1	1	(2.2%)	1
Leading to discontinuation	1	(7.1%)	1	2	(12.5%)	3	1	(6.7%)	1	3	(9.7%)	4	4	(8.9%)	5
Serious	1	(7.1%)	1	2	(12.5%)	2	1	(6.7%)	1	3	(9.7%)	3	4	(8.9%)	4
Extrapyramidal syndrome	6	(42.9%)	11	3	(18.8%)	5	3	(20.0%)	4	6	(19.4%)	9	12	(26.7%)	20
Prolactin related AE	5	(35.7%)	5	3	(18.8%)	3	1	(6.7%)	2	4	(12.9%)	5	9	(20.0%)	10
Failure to thrive	1	(7.1%)	1	2	(12.5%)	2	3	(20.0%)	3	5	(16.1%)	5	6	(13.3%)	6
Subject with AE related to study drug	8	(57.1%)	28	10	(62.5%)	19	7	(46.7%)	19	17	(54.8%)	38	25	(55.6%)	66
Death	0			0			0			0			0		
Leading to discontinuation	0			1	(6.3%)	1	0			1	(3.2%)	1	1	(2.2%)	1
Serious	0			1	(6.3%)	1	0			1	(3.2%)	1	1	(2.2%)	1
Extrapyramidal syndrome	6	(42.9%)	11	3	(18.8%)	5	3	(20.0%)	4	6	(19.4%)	9	12	(26.7%)	20
Prolactin related AE	5	(35.7%)	5	3	(18.8%)	3	1	(6.7%)	2	4	(12.9%)	5	9	(20.0%)	10
Failure to thrive	1	(7.1%)	1	1	(6.3%)	1	3	(20.0%)	3	4	(12.9%)	4	5	(11.1%)	5

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.5-7　体重（50 kg 未満、50 kg 以上）別有害事象及び副作用の発現状況（長期試験）

Safety Analysis Set
Weight < 50 kg

	DB-PLCB N = 15			DB-8MG N = 9			DB-16MG N = 9			DB-Active N = 18			Overall N = 33		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	15	(100.0%)	103	9	(100.0%)	80	6	(66.7%)	29	15	(83.3%)	109	30	(90.9%)	212
Death	0			0			0			0			0		
Leading to discontinuation	2	(13.3%)	2	0			0			0			2	(6.1%)	2
Serious	3	(20.0%)	3	1	(11.1%)	1	0			1	(5.6%)	1	4	(12.1%)	4
Extrapyramidal syndrome	7	(46.7%)	11	6	(66.7%)	12	2	(22.2%)	4	8	(44.4%)	16	15	(45.5%)	27
Prolactin related AE	5	(33.3%)	5	4	(44.4%)	4	0			4	(22.2%)	4	9	(27.3%)	9
Failure to thrive	1	(6.7%)	1	0			1	(11.1%)	1	1	(5.6%)	1	2	(6.1%)	2
Subject with AE related to study drug	10	(66.7%)	34	8	(88.9%)	19	5	(55.6%)	16	13	(72.2%)	35	23	(69.7%)	69
Death	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Serious	0			0			0			0			0		
Extrapyramidal syndrome	7	(46.7%)	11	6	(66.7%)	12	2	(22.2%)	4	8	(44.4%)	16	15	(45.5%)	27
Prolactin related AE	4	(26.7%)	4	4	(44.4%)	4	0			4	(22.2%)	4	8	(24.2%)	8
Failure to thrive	1	(6.7%)	1	0			1	(11.1%)	1	1	(5.6%)	1	2	(6.1%)	2

Weight >= 50 kg

	DB-PLCB N = 21			DB-8MG N = 28			DB-16MG N = 24			DB-Active N = 52			Overall N = 73		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	18	(85.7%)	211	25	(89.3%)	154	23	(95.8%)	198	48	(92.3%)	352	66	(90.4%)	563
Death	0			0			2	(8.3%)	2	2	(3.8%)	2	2	(2.7%)	2
Leading to discontinuation	2	(9.5%)	2	3	(10.7%)	4	2	(8.3%)	2	5	(9.6%)	6	7	(9.6%)	8
Serious	5	(23.8%)	6	4	(14.3%)	4	4	(16.7%)	4	8	(15.4%)	8	13	(17.8%)	14
Extrapyramidal syndrome	10	(47.6%)	23	7	(25.0%)	12	9	(37.5%)	12	16	(30.8%)	24	26	(35.6%)	47
Prolactin related AE	4	(19.0%)	4	6	(21.4%)	6	5	(20.8%)	6	11	(21.2%)	12	15	(20.5%)	16
Failure to thrive	3	(14.3%)	4	7	(25.0%)	7	3	(12.5%)	3	10	(19.2%)	10	13	(17.8%)	14
Subject with AE related to study drug	14	(66.7%)	46	17	(60.7%)	46	15	(62.5%)	29	32	(61.5%)	75	46	(63.0%)	121
Death	0			0			0			0			0		
Leading to discontinuation	0			2	(7.1%)	2	0			2	(3.8%)	2	2	(2.7%)	2
Serious	0			1	(3.6%)	1	0			1	(1.9%)	1	1	(1.4%)	1
Extrapyramidal syndrome	10	(47.6%)	23	7	(25.0%)	12	7	(29.2%)	9	14	(26.9%)	21	24	(32.9%)	44
Prolactin related AE	4	(19.0%)	4	6	(21.4%)	6	5	(20.8%)	6	11	(21.2%)	12	15	(20.5%)	16
Failure to thrive	1	(4.8%)	1	4	(14.3%)	4	3	(12.5%)	3	7	(13.5%)	7	8	(11.0%)	8

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

表 2.7.4.5-8　発症回数（1 回、2 回以上）別有害事象及び副作用の発現状況（長期試験）

Safety Analysis Set
Number of Episodes = 1

	DB-PLCB N = 29			DB-8MG N = 32			DB-16MG N = 22			DB-Active N = 54			Overall N = 83		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	27	(93.1%)	255	29	(90.6%)	200	21	(95.5%)	161	50	(92.6%)	361	77	(92.8%)	616
Death	0			0			2	(9.1%)	2	2	(3.7%)	2	2	(2.4%)	2
Leading to discontinuation	4	(13.8%)	4	3	(9.4%)	4	2	(9.1%)	2	5	(9.3%)	6	9	(10.8%)	10
Serious	8	(27.6%)	9	4	(12.5%)	4	4	(18.2%)	4	8	(14.8%)	8	16	(19.3%)	17
Extrapyramidal syndrome	15	(51.7%)	32	9	(28.1%)	14	7	(31.8%)	10	16	(29.6%)	24	31	(37.3%)	56
Prolactin related AE	8	(27.6%)	8	9	(28.1%)	9	3	(13.6%)	4	12	(22.2%)	13	20	(24.1%)	21
Failure to thrive	4	(13.8%)	5	7	(21.9%)	7	3	(13.6%)	3	10	(18.5%)	10	14	(16.9%)	15
Subject with AE related to study drug	19	(65.5%)	70	21	(65.6%)	54	14	(63.6%)	34	35	(64.8%)	88	54	(65.1%)	158
Death	0			0			0			0			0		
Leading to discontinuation	0			2	(6.3%)	2	0			2	(3.7%)	2	2	(2.4%)	2
Serious	0			1	(3.1%)	1	0			1	(1.9%)	1	1	(1.2%)	1
Extrapyramidal syndrome	15	(51.7%)	32	9	(28.1%)	14	6	(27.3%)	8	15	(27.8%)	22	30	(36.1%)	54
Prolactin related AE	7	(24.1%)	7	9	(28.1%)	9	3	(13.6%)	4	12	(22.2%)	13	19	(22.9%)	20
Failure to thrive	2	(6.9%)	2	4	(12.5%)	4	3	(13.6%)	3	7	(13.0%)	7	9	(10.8%)	9

Number of Episodes >= 2

	DB-PLCB N = 5			DB-8MG N = 4			DB-16MG N = 11			DB-Active N = 15			Overall N = 20		
	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e	n	(%)	e
Subject with any AE	4	(80.0%)	32	4	(100.0%)	28	8	(72.7%)	66	12	(80.0%)	94	16	(80.0%)	126
Death	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Serious	0			1	(25.0%)	1	0			1	(6.7%)	1	1	(5.0%)	1
Extrapyramidal syndrome	2	(40.0%)	2	3	(75.0%)	6	4	(36.4%)	6	7	(46.7%)	12	9	(45.0%)	14
Prolactin related AE	1	(20.0%)	1	1	(25.0%)	1	2	(18.2%)	2	3	(20.0%)	3	4	(20.0%)	4
Failure to thrive	0			0			1	(9.1%)	1	1	(6.7%)	1	1	(5.0%)	1
Subject with AE related to study drug	4	(80.0%)	8	3	(75.0%)	7	6	(54.5%)	11	9	(60.0%)	18	13	(65.0%)	26
Death	0			0			0			0			0		
Leading to discontinuation	0			0			0			0			0		
Serious	0			0			0			0			0		
Extrapyramidal syndrome	2	(40.0%)	2	3	(75.0%)	6	3	(27.3%)	5	6	(40.0%)	11	8	(40.0%)	13
Prolactin related AE	1	(20.0%)	1	1	(25.0%)	1	2	(18.2%)	2	3	(20.0%)	3	4	(20.0%)	4
Failure to thrive	0			0			1	(9.1%)	1	1	(6.7%)	1	1	(5.0%)	1

- Abbreviations: AE, adverse event.
- Adverse events related to study drug are defined as adverse events reported as 'Definite', 'Probable', 'Possible', 'Unassessable' or with a missing drug-event relationship.
- N is the number of subjects in the safety population. n and % are respectively the number and proportion of subjects experiencing the event. e is the number of events.
- Subjects experiencing multiple adverse events are counted only once in each category.
- Treatment group at confirmatory study: DB-PLCB = Placebo; DB-8MG = DSP-5423 8 mg; DB-16MG = DSP-5423 16 mg; DB-Active = DSP-5423 8 mg or 16 mg; Overall = Placebo, DSP-5423 8 mg or 16 mg.

(3) 成人

ロナセン経口剤は成人の統合失調症を効能・効果として市販されている(2.7.4.6 項参照)。成人と小児での安全性プロファイルを比較検討するため、成人の統合失調症を効能・効果とした申請時（初回申請時）に提出した資料（1.13.1.1 参照）のうち、グループ B（平成 9 年から施行された GCP 省令に従い有害事象を収集した臨床試験のグループ）として集計した第 3 相試験(AD5423-301-5 試験及び AD5423-308-17 試験)と長期投与試験(AD5423-302-8 試験及び AD5423-302-12 試験）の 4 試験での結果を以下に示す。なお、第 3 相試験では、実薬対照をハロペリドール又はリスペリドンとし、ロナセン経口剤を 1 日 2 回食後に投与した。漸増法でロナセン経口剤を 8～24 mg/日（開始用量 8 mg/日、増量幅 4 mg/日）8 週間投与した。長期投与試験では、ロナセン経口剤を 4～24 mg/日、1 日 2 回 26～52 週間投与した。

有害事象の発現状況を表 2.7.4.5-9 に、2.7.4.1.1.2.1 項で定義した注目すべき有害事象に該当する個々の事象の発現割合を表 2.7.4.5-10～表 2.7.4.5-28 に示す。初回申請時の有害事象を MedDRA/J ver.19.1 に読み替え、注目すべき有害事象の定義（MedDRA/J ver.19.1）に従い集計し、表中へは初回申請時と同様の MedDRA/J ver.7.0 で表示した。なお、注目すべき有害事象に該当する個々の事象の発現割合は、第 3 相試験のロナセン経口剤群合計（285 名）及びリスペリドン群（145 名）、長期投与試験のロナセン経口剤合計（382 名）について示した。ロナセン経口剤の初回申請時の 4 試験で、注目すべき有害事象のうち、肺塞栓症・深部静脈血栓症関連有害事象の発現はなかった。

表 2.7.4.5-9　成人での有害事象の発現状況（ロナセン経口剤の初回申請資料）

	第 III 相試験（ハロペリドール）		第 III 相試験（リスペリドン）		8 週投与 LNS 合計	長期投与合計	LNS 合計
	LNS	HPD	LNS	RIS			
安全性評価例数	129	132	156	145	285	382	667
有害事象発現例数	120	126	153	143	273	370	643
有害事象発現率（%）	93.0	95.5	98.1	98.6	95.8	96.9	96.4
95%信頼区間下限（%）	87.2	90.4	94.5	95.1	92.8	94.6	94.7
95%信頼区間上限（%）	96.8	98.3	99.6	99.8	97.8	98.4	97.7
重篤な有害事象発現例数	3	4	3	2	6	25	31
重篤な有害事象発現率（%）	2.3	3.0	1.9	1.4	2.1	6.5	4.6
副作用発現例数	106	110	148	142	254	264	518
副作用発現率（%）	82.2	83.3	94.9	97.9	89.1	69.1	77.7
95%信頼区間下限（%）	74.5	75.9	90.1	94.1	84.9	64.2	74.3
95%信頼区間上限（%）	88.3	89.3	97.8	99.6	92.5	73.7	80.8

LNS：ロナセン錠、HPD：ハロペリドール、RIS：リスペリドン
ロナセン経口剤の初回申請資料：1.13.1.1CTD2.5