STATISTICAL ANALYSIS PLAN

Protocol No.:	SPD489-348
Protocol Title:	A Phase 3, Open-label, Multicenter, 12-Month Safety and Tolerability Study of SPD489 in Preschool Children Aged 4-5 Years Diagnosed with Attention-deficit/Hyperactivity Disorder
Drug:	SPD489, Lisdexamfetamine dimesylate
Sponsor:	Shire Development LLC and International Affiliates 1200 Morris Drive, Wayne, PA 19087 USA
Version No. and Date	Amendment 2, 20 Oct 2017

Version No:	Document History Description of Update	Author(s)	Effective Date
Version 1.0	First Version	[redacted]	04 Jun 2018
Version 1.1	Version 1.1 -Addition of schedule of procedure, study design and visit mapping for those enrolled under the original protocol. -Imputation method added for those with a missing last dose date. -Removal of the following text: 'Subjects that do not return the investigational product but return to the site for a following visit will have zero (0) capsule returned entered into the database. In this case, it will be assumed for analysis purposes that all capsules were ingested.'	[redacted]	17 Jul 2019

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LIST OF ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS-IV	ADHD Rating Scale-IV
AE	adverse event
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CGI-I	Clinical Global Impression – Global Improvement
CGI-S	Clinical Global Impression – Severity of Illness
CI	Confidence interval
CSHQ	Children's Sleep Habits Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
DINFC	date of informed consent
DMC	data monitoring committee
DOB	Date of birth
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition – Text Revision
eCRF	electronic case report form
ECG	electrocardiogram
ET	early termination
FAS	Full Analysis Set
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
PCI	potentially clinically important
PT	preferred term
QTcB	QT Interval Corrected for Heart Rate using Bazett's Formula
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
SAP	statistical analysis plan
SD	standard deviation
SI	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety, tolerability and efficacy data as described in the final study protocol SPD489-348 Amendment 2.0 dated 20 Oct 2017. Specifications for tables, figures, and listings are contained in a separate document.

2. STUDY DESIGN

2.1 General Study Design

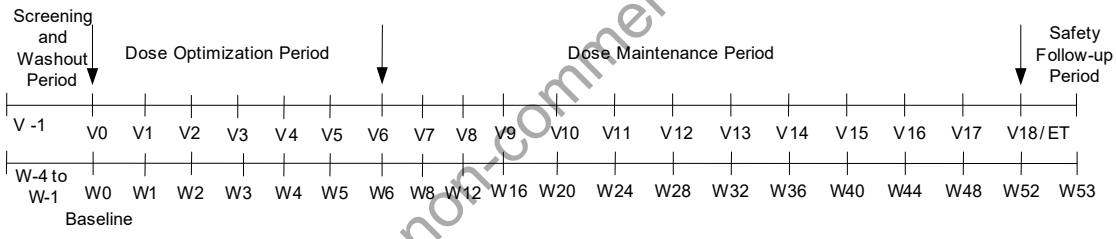
Approximately 100 subjects will be enrolled in this long-term, open-label study to evaluate safety and tolerability of SPD489, administered as a daily morning dose in the treatment of children 4-5 years of age with attention-deficit/hyperactivity disorder (ADHD). SPD489 is proposed to be provided in 5, 10, 15, 20, and 30 mg capsules.

This study will enroll subjects who participated in an antecedent SPD489 study (SPD489-211 or SPD489-347) or through direct enrollment. Subjects entering into this study will be classified as either a roll-over subject or a direct-enrolled subject, as defined below:

- Roll-over subject: Subject completed the antecedent study (SPD489-211 or SPD489-347)
- Directly enrolled subject: Subject is directly enrolled in this study and did not participate in antecedent study SPD489-211 or SPD489-347

The study design consists of up to 4 periods: Screening and Washout, Dose Optimization, Dose Maintenance, and Safety Follow-up. These subjects will be required to visit the site up to 20 times over a 57-week period. The study design is demonstrated below in Figure 1:

Figure 1 Study Design Flow Chart



ET=early termination; V=visit; W=week.

Subjects will be screened at Visit -1 to establish eligibility for study participation. For roll-over subjects, the EOS visit in the antecedent SPD489-347 study will serve as the Screening visit for SPD489-348. Screening assessments (vital signs, height, weight, clinical laboratory tests, and electrocardiograms (ECGs)) must be repeated for this study if more than 30 days have elapsed since the conclusion of the antecedent study. The Washout Period should be initiated after the clinical laboratory test results and 12-lead ECG results have been received and reviewed by the investigator. The roll-over subjects, the follow-up call for the antecedent SPD489-347 study will serve as the wash-out call for the SPD489-348 study. During washout, a subject's current prohibited medications (if applicable) will be discontinued for a period of a minimum of 5 times the half-life of the medication.

During the Dose Optimization Period (Visits 1 to 6), the investigator may titrate subjects to their optimal dose of SPD489 based upon treatment-emergent adverse events (TEAEs) and dosing guidelines. If optimal dose is well tolerated and, in the opinion of the investigator, the subject

would potentially receive additional symptom reduction, the subject may be titrated to the next allowed dose.

Subjects then enter the Dose Maintenance Period (Visits 7 to 18/ET) where they continue daily morning treatment for an additional 48 weeks. Subjects will attend the clinic every 4 weeks for procedures to be performed.

The Safety follow-up period is 7 days + 3 days from the last dose of investigational product.

Subjects that are enrolled under the original protocol SPD489-348 dated 21 Oct 2014 are classified as either an "A" Subject or a "B" Subject, determined by the need to retitrate the SPD489 dose, defined as follows:

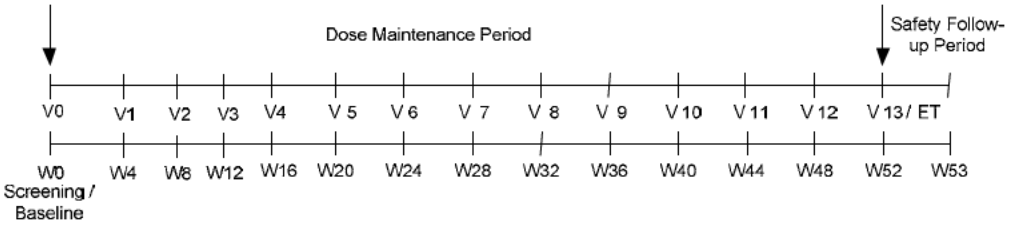
- "A" Subjects are subjects on a known dose of SPD489, classified as subjects who completed the final visit of the treatment phase of an unblinded antecedent study (SPD489-211) who are directly entering this study ≤3 days after the last dose of study medication in the previous study.
- "B" Subjects are subjects who require dose titration, classified as subjects who completes at least the dose optimization and follow up of the blinded antecedent study (SPD489-347) OR those subjects who completed the final visit of the treatment phase of the unblinded antecedent study (SPD489-211) and did not enroll in this study within 3 days.

For "B" Subjects, screening assessments (physical examination, vital signs, height, weight, clinical laboratory tests, and electrocardiograms (ECGs)) must be repeated for this study if more than 30 days have elapsed since the conclusion of the antecedent study.

During the Dose Maintenance Period for both "A" and "B" Subjects, the investigator may make further dose adjustments based upon treatment-emergent adverse events (TEAEs) and clinical judgment.

The study design that "A" Subjects will follow consists of up to 2 periods: Dose Maintenance and Safety Follow-up. These subjects will be required to visit the site up to 14 times over a 53-week period. Baseline procedures, at Week 0, will be assessed at the final dose maintenance visit of the antecedent study. The study design is demonstrated below in Figure 2.

Figure 2 Study Design Flow Chart for "A" Subjects

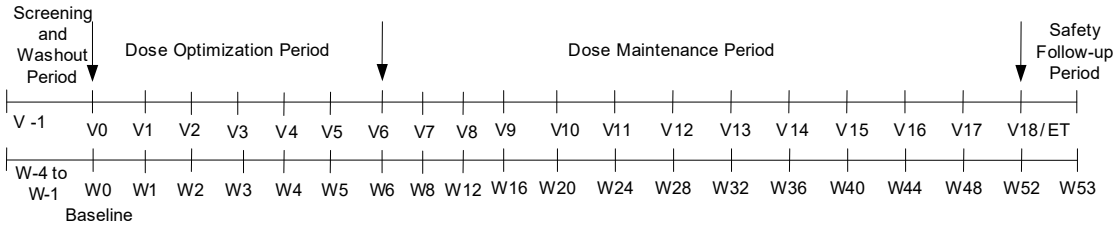


ET=early termination; V=visit; W=week.

The study design that "B" Subjects will follow consists of up to 4 periods: Screening and Washout, Dose Optimization, Dose Maintenance, and Safety Follow-up. These subjects will be

required to visit the site up to 20 times over a 57-week period. The study design is demonstrated below in Figure 3.

Figure 3 Study Design Flow Chart for "B" Subjects



ET=early termination; V=visit; W=week.

2.2 Randomization

There is no randomization for this study. All subjects will receive open-label SPD489 during this study.

2.3 Blinding

Not applicable.

2.4 Schedule of Assessments

Table 1, Table 2 and Table 3 below present a schematic of the study procedures.

Table 1 Schedule of Assessments

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period												Safety Follow-up
Visit [a]	-1 (Screening)[b]	Phone Call[c]	Visit 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
Informed consent/assent	✓																					
Inclusion/ exclusion criteria[d]	✓	✓	✓																			
Psychiatric Evaluation (utilizing the K-SADS-PL)[e]	✓																					
Peabody Picture Vocabulary Test, Fourth	✓																					
Demographics	✓																					
Medical and medication history	✓																					
Physical examination [f]	✓		✓																			
Vital signs [f,g]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Height [f,h]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 1 Schedule of Assessments

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period												Safety Follow-up
Visit [a]	-1 (Screening)[b]	Phone Call[c]	Visit 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
Body weight [f,h]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Clinical laboratory test[f,i]	✓		✓									✓							✓		✓	
12-lead ECG [f,j]	✓		✓	✓	✓	✓	✓	✓	✓		✓			✓			✓			✓	✓	
ADHD-RS-IV [k]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI-I [k]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI-S[e,k]			✓																			
CSHQ [k]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
C-SSRS [l]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Sleep diary[m]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Suitability of subject to remain in study[n]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigator dose assessment				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Access IWRS	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 1 Schedule of Assessments

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period												Safety Follow-up
Visit [a]	-1 (Screening)[b]	Phone Call[c]	Visit 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
Investigational product distributed			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigational product returned				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product compliance				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 1 Schedule of Assessments

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period												Safety Follow-up
Visit [a]	-1 (Screening)[b]	Phone Call[c]	Visit 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371

[a] Visit Window for Visits 1-6 is ±3 days, and Visit Window for Visits 7-17 is ±5 days [in reference to the Visit 0 date]; Visit Window for Visit 18 is ±5 days; Visit Window for Safety Follow-up Telephone call is + 3 days.
[b] For roll-over subjects, the Screening (visit -1) is the same day as the End of Study Visit for the antecedent SPD489-347 study
[c] Following successful screening, a study center representative will contact the subject/parent/LAR to provide instruction on discontinuing any prohibited medication for the Washout Period (if applicable). For roll-over subjects, the Wash-out phone call is the same day as the Follow-up phone call for the antecedent SPD489-347 study
[d] Inclusion/exclusion criteria must be reviewed at the Washout Telephone Call and at Visit 0.
[e] For direct-enrolled subjects only.
[f] An abbreviated physical examination, vital signs, height, weight, clinical laboratory assessments, and ECG are required to be repeated if > 30 days have elapsed since the Screening visit. The results must be obtained and reviewed by the investigator prior to determining eligibility and the subject being enrolled at (Visit 0).
[g] Includes oral or tympanic temperature, sitting blood pressure, pulse, and respiratory rate. Measurement of temperature and respiratory rate will be performed at the Screening Visit (Visit -1) only.
Measurement of blood pressure and pulse will be collected 3 times after subjects have remained sitting for a minimum of 5 minutes(with approximately 2 minutes in between each collection) using a manual cuff. The average of each set of 3 measurements will be used to determine continued participation in the study. Blood pressure, pulse and respiratory rate will be determined after subjects have remained seated for approximately 5 minutes. Refer to Protocol Section 4.4.1
[h] Height and weight to be measured without shoes.
[i] Clinical laboratory tests will include hematology, chemistry, endocrinology, and urinalysis. Patients will have the option for blood draws to be collected by a home health care professional at their home. Home draws have a ±1 day window from study visit date, with the exception of Visit 18/ET home draw which has a -1 day window.
[j] A single ECG will be collected at Screening (Visit -1), Visits 0, 3, 6, 9, 12, 15and 18/ET
[k] Scales to be completed by same rater whenever possible
[l] For roll-over subjects, C-SSRS pediatric/cognitively impaired "Since Last Visit" version is completed for all visits. The scale will be compared to the C-SSRS pediatric/cognitively impaired "Lifetime recent" from the antecedent study. If subject is directly enrolled, C-SSRS pediatric/cognitively impaired "Lifetime Recent" version is completed at the Screening Visit (Visit -1). C-SSRS pediatric/cognitively impaired "Since Last Visit" version completed for all subsequent visits
[m] Sleep diary to be completed by parent/LAR. Sleep diaries will be dispensed at Visits 0-17 and collected at Visits 1-18.
[n] Includes assessment of decreased appetite
ADHD-RS-IV=ADHD Rating Scale-IV; CGI-I=Clinical Global Impressions-Global Improvement; CGI-S=Clinical Global Impressions-Severity of Illness; CSHQ=Children's Sleep Habits Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale- Pediatric/Cognitively Impaired; ECG=electrocardiogram; ET=early termination; IWRS=Interactive Web Response System

Table 2 Schedule of Assessments for "A" Subjects

Period	Dose Maintenance Period														Safety Follow-up
Visit [a]	Visit 0[b]	1	2	3	4	5	6	7	8	9	10	11	12	13/ET	Telephone Call
Assessment Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	0	28	56	84	112	140	168	196	224	252	280	308	336	364	371
Informed consent/assent	✓														
Inclusion/exclusion criteria[c]	✓														
Demographics[d]	✓														
Medical and medication history	✓														
Physical examination	✓														
Vital signs [e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Height [f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Body weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Clinical laboratory test[g]	✓						✓							✓	
12-lead ECG[h]	✓			✓			✓			✓			✓	✓	
ADHD-RS-IV [i]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI-I [i]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CSHQ [i]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
C-SSRS [j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Sleep diary [k]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Suitability of subject to remain in study		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigator dose assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

Table 2 Schedule of Assessments for "A" Subjects

Period	Dose Maintenance Period														Safety Follow-up
Visit [a]	Visit 0[b]	1	2	3	4	5	6	7	8	9	10	11	12	13/ET	Telephone Call
Assessment Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	0	28	56	84	112	140	168	196	224	252	280	308	336	364	371
Access IWRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product distributed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigational product returned		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a] Visit Window for Visits 1-6 is ± 2 days, and Visit Window for Visits 7-17 is ±5 days [in reference to the Visit 0 date]; Visit Window for Visit 18 is +5 days; Visit Window for Safety Follow-up Telephone call is + 2 days.
[b] Visit 0 is the same day as the End of Study Visit for the antecedent study
[c] Inclusion/exclusion criteria must be reviewed at the Washout Telephone Call and at Visit 0.
[d] Demographic data will be pulled programmatically from antecedent study.
[e] Includes oral or tympanic temperature, sitting blood pressure, pulse, and respiratory rate. Measurement of temperature and respiratory rate will be performed as part of the End of Study Visit of the antecedent study. Measurement of blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) using the provided automated cuff. The average of each set of 3 measurements will be used to determine continued participation in the study. Blood pressure, pulse and respiratory rate will be determined after subjects have remained seated for approximately 5 minutes.
[f] Height to be measured without shoes.
[g] Clinical laboratory tests will include hematology, chemistry, endocrinology, and urinalysis.
[h] A single ECG will be collected at, Visits 0, 3, 6, 9, 12, 15 and 18/ET
[i] Scales to be completed by same rater whenever possible.
[j] C-SSRS pediatric/cognitively impaired "Since Last Visit" version is completed for all visits. The scale will be compared to the C-SSRS pediatric/cognitively impaired "Baseline" from the antecedent study.
[k] Sleep diary to be completed by parent/LAR. Sleep diaries will be dispensed at Visits 0-17 and collected at Visits 1-18.
ADHD-RS-IV=ADHD Rating Scale-IV; CGI-I=Clinical Global Impressions-Global Improvement; CGI-S=Clinical Global Impressions-Severity of Illness; CSHQ=Children's Sleep Habits Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale- Pediatric/Cognitively Impaired; ECG=electrocardiogram; ET=early termination; IWRS=Interactive Web Response System

Table 3 Schedule of Assessments for "B" Subjects

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period												Safety Follow-up
Visit [a]	-1 (Screening)	Phone Call	Visit0 [b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
Informed consent/assent	✓																					
Inclusion/ exclusion criteria [c]	✓	✓	✓																			
Demographics [d]	✓																					
Medical and medication history	✓																					
Physical examination [e]	✓		✓																			
Vital signs [d,f]	✓		✓[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Height [d,g]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Body weight [d]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Clinical laboratory test [d,h]	✓		✓[m]									✓							✓		✓	
12-lead ECG [d,i]	✓		✓[m]	✓	✓	✓	✓	✓	✓		✓			✓			✓			✓	✓	
ADHD-RS-IV [j]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI-I [j]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CSHQ [j]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 3 Schedule of Assessments for "B" Subjects

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period												Safety Follow-up
Visit [a]	-1 (Screening)	Phone Call	Visit0 [b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
C-SSRS [k]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Sleep diary [l]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Suitability of subject to remain in study				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigator dose assessment				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Access IWRS	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product distributed			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigational product returned				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product compliance				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3 Schedule of Assessments for "B" Subjects

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period												Safety Follow-up
Visit [a]	-1 (Screening)	Phone Call	Visit0 [b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371

[a] Visit Window for Visits 1-6 is ± 2 days, and Visit Window for Visits 7-17 is ±5 days [in reference to the Visit 0 date]; Visit Window for Visit 18 is +5 days; Visit Window for Safety Follow-up Telephone call is + 2 days.
[b] Visit 0 is the same day as the End of Study Visit for the antecedent study
[c] Following successful screening, a study center representative will contact the subject/parent/LAR to provide instruction on discontinuing any prohibited medication for the Washout Period (if applicable). Inclusion/exclusion criteria must be reviewed at the Washout Telephone Call and at Visit 0.
[d] Demographic data will be pulled programmatically from antecedent study.
[e] A physical examination, vital signs, height, weight, clinical laboratory assessments, and ECG are required to be repeated if > 30 days have elapsed since the End of Study visit of the antecedent study. The results must be reviewed by the Investigator prior to the subject being enrolled at (Visit 0).
[f] Includes oral or tympanic temperature, sitting blood pressure, pulse, and respiratory rate. Measurement of temperature and respiratory rate will be performed at the Screening Visit (Visit -1) only. Measurement of blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) using the provided automated cuff. The average of each set of 3 measurements will be used to determine continued participation in the study. Blood pressure, pulse and respiratory rate will be determined after subjects have remained seated for approximately 5 minutes.
[g] Height to be measured without shoes.
[h] Clinical laboratory tests will include hematology, chemistry, endocrinology, and urinalysis.
[i] A single ECG will be collected at Screening (Visit -1), Visits 0, 3, 6, 9, 12, 15 and 18/ET
[j] Scales to be completed by same rater whenever possible.
[k] C-SSRS pediatric/cognitively impaired "Since Last Visit" version is completed for all visits. The scale will be compared to the C-SSRS pediatric/cognitively impaired "Baseline" from the antecedent study.
[l] Sleep diary to be completed by parent/LAR. Sleep diaries will be dispensed at Visits 0-17 and collected at Visits 1-18.
[m] An abbreviated physical examination and all clinical laboratory tests must be repeated at Visit 0 if >30 days have elapsed since the Screening Visit. Results must be obtained and reviewed prior to determining eligibility.
ADHD-RS-IV=ADHD Rating Scale-IV; CGI-I=Clinical Global Impressions-Global Improvement; CGI-S=Clinical Global Impressions-Severity of Illness; CSHQ=Children's Sleep Habits Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale- Pediatric/Cognitively Impaired; ECG=electrocardiogram; ET=early termination; IWRS=Interactive Web Response System

2.5 Determination of Sample Size

Approximately 100 subjects will be enrolled into this study to ensure that at least 50 subjects are exposed to SPD489 for one year. Subjects will enroll into this study from an antecedent study (SPD489-211 or SPD489-347) or directly enroll onto this study without participating in either antecedent study.

The sample size for this study is not based on statistical considerations.

2.6 Multiplicity Adjustments for Type I Error Control

Not applicable as there will be no hypothesis testing for this study.

3. OBJECTIVES

3.1 Primary Objectives

The primary objective of this study is to evaluate the long-term safety of SPD489 administered as a daily morning dose (proposed as 5, 10, 15, 20, and 30 mg/day) in preschool children (4-5 years of age inclusive) diagnosed with ADHD.

The evaluation of safety and tolerability will be based on the occurrence of TEAEs, specific evaluation of blood pressure, pulse, weight, height, clinical laboratory evaluations, ECG results, and sleep assessments.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To describe the long-term efficacy of SPD489 using the clinician-administered Attention-deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) Preschool Version.
- To describe the long-term efficacy of SPD489 using global clinical measures of improvement, as measured by the Clinical Global Impression – Global Improvement (CGI-I).

4. SUBJECT POPULATION SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed an informed consent for study SPD489-348.

4.2 Enrolled Set

The Enrolled Set will consist of all subjects who have been dispensed SPD489 at the Baseline Visit (Visit 0) in study SPD489-348. The screen failures will not be considered enrolled subjects and will not be included in the Enrolled Set.

4.3 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who have taken at least 1 dose of investigational product in study SPD489-348.

4.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the Safety Analysis Set who have at least 1 post-dose ADHD-RS-IV Preschool Version total score assessment in study SPD489-348.

5. SUBJECT DISPOSITION

Subject disposition data will be summarized by treatment group (SPD489 or Placebo) of the antecedent studies, those who were directly enrolled and overall.

A listing of all screen failures (i.e., subjects who were screened but not treated) will be presented along with reasons for screen failure and details of any AEs.

The number of subjects included in each subject set (i.e., Screened, Enrolled, Safety and FAS) will be summarized.

The number and percentage of subjects who completed and prematurely discontinued during the study will be presented for the Screened Set. Reasons for premature discontinuation from the study as recorded on the termination page of the electronic case report form (eCRF) will be summarized (number and percentage) for the Safety Analysis Set. All subjects who prematurely discontinued during the study will be listed with discontinuation reason for the Screened Set.

The number of subjects enrolled and completed will be tabulated by site. In addition, the duration of enrollment, in days, will be summarized for each site and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site - the first date of informed consent for any subject at that site + 1).

6. PROTOCOL DEVIATIONS

Protocol deviations will be recorded by the site separately from the clinical database. The contract research organization will classify the protocol deviations per the agreed protocol deviation plan. The Shire study team will review the protocol deviations and their classification throughout the study and before database lock.

Confirmed protocol deviations will be documented in the Protocol Deviation tracker for the study. A summary of the number and percentage of subjects in the Safety Analysis Set with protocol deviations will be produced by treatment group of the antecedent studies, directly enrolled and overall.

All protocol deviation data will be listed for the Safety Analysis Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics data collected in the antecedent studies will be summarized by treatment group of the antecedent studies and overall for the Safety Analysis Set and FAS. For those directly enrolled, demographic and baseline characteristics are as collected in the SPD489 CRF will be summarized.

The following demographic characteristics will be summarized in the following order in the tables: age (at date of informed consent for antecedent study), current age (at date of informed consent for SPD489-348 study), sex, ethnicity, race, weight, height, body mass index (BMI) and BMI category. Baseline characteristic to be summarized include Peabody Picture Vocabulary Test standard score, CGI-S and ADHD subtypes. Continuous variables will be summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by the number of subjects in each category and the percentage of subjects out of the total in the respective analysis set.

Antecedent study age will be calculated as the difference between date of birth (DOB) and date of informed consent (DINFC) for the antecedent study and current age will be calculated using date of informed consent for SPD489-348, truncated to months then minus 1 if the day of birth is later than the day of informed consent. This number is then divided by 12 and truncated to obtain the age in years. The formula in SAS programming language is as follows:

```
Age = floor((intck('month', DOB, DINFC) - (day(DINFC) < day(DOB))) / 12)
```

Height and weight will be collected and used to calculate BMI using the following formula:

$$\text{BMI} = \frac{\text{Weight [kg]}}{(\text{Height [m]})^2}$$

BMI should be rounded to 1 decimal place for reporting. BMI categories will be derived using the Centers for Disease Control and Prevention (CDC) BMI percentiles for children and adolescents: Underweight – BMI less than the 5th percentile; Healthy Weight – BMI 5th percentile up to less than the 85th percentile; Overweight – BMI 85th percentile to less than the 95th percentile; Obese – BMI greater than or equal to the 95th percentile.

All demographic and baseline characteristics data (baseline information from the antecedent studies and data collected during this study for Peabody Picture Vocabulary Test standard score, CGI-S and ADHD subtypes) will be listed for the Safety Analysis Set.

7.2 Medical History

Medical history is collected at Screening Visit (Visit -1). Any new medical history which arose after the recording of the medical history in the antecedent study should be recorded for roll-over subjects. Medical history will be listed for the Safety Analysis Set.

Prior and Ongoing psychiatric evaluation will be established with the Screening Visit (Visit -1) interview for directly enrolled subjects using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version-Diagnostic Interview (K-SADS-PL). Both assessment results will be listed for the Safety Analysis Set.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational product

Under the original Protocol SPD489-348 dated 21 Oct 2014, a subject from the open-label antecedent study (SPD489-211) will enter this study on their optimal dose, if entering this study within 3 days. However, if a subject is entering this study from the double-blind antecedent study (SPD489-347), or the subject does not immediately enter following the dose maintenance period of the unblinded study (SPD489-211), then the subject will begin dosing at 5mg of SPD489 and should be titrated in a stepwise fashion until an optimal dose is reached.

Under Protocol Amendment dated 20 Oct 2017, all subjects will begin dosing at 5mg of SPD489 and should be titrated in a stepwise fashion until optimal dose is reached.

Exposure to investigational product for the Safety Analysis Set will be summarized by treatment group of the antecedent studies, directly enrolled and overall. The following statistics will be calculated by visit and period for the investigational product:

- Days of dosing: number of days on which dose information was available and non-zero (derived using date of last dose from bottle – date of first dose from bottle +1)
- Total dose (mg): Total number of capsules taken × dose level
- Average daily dose (mg/day): the total dose / total days of dosing
- Cumulative dose (mg): sum of total dose since start of treatment

The following overall statistics will also be calculated for the investigational product:

- Total days of dosing: sum of the days of dosing
- Duration of exposure in weeks: the total days of dosing / 7
- Duration of exposure: categorical summary in 4 week intervals
- Total dose (mg): Total number of capsules taken × dose level
- Average daily dose (mg/day): the total dose / total days of dosing
- Optimized dose: dose during the dose maintenance period

An appropriate statistical summary will be applied in order to present each of the above statistical quantities.

In addition, person-time (overall total exposure in years) will be derived. It is calculated as total number of days in which the investigational product was taken for each subject and then sum over all subjects for the whole duration of the study and then divided by 365.25. Dosing information will be listed that will present exposure information, such as total dose, average daily dose, optimized dose level, etc.

If a subject is lost to follow-up without returning the leftover investigational product, and without providing subsequent safety information, then the subject's dose information will be

treated as missing. In particular, for the subjects lost to follow up after the Baseline Visit (Visit 0), we will not assume any ingestion of the investigational product unless there is a post-baseline safety assessment.

8.2 Measurement of Treatment Compliance

Investigational product dosing compliance is defined as the total number of capsules actually taken by a subject during the study divided by the number of capsules expected to be taken during the study multiplied by 100. The total number of capsules taken is calculated by the total number of capsules dispensed minus the number of capsules returned. If a bottle is not returned, the number of capsules returned for that bottle will be imputed to 0. The number of capsules expected to be taken is calculated as the number of days in the treatment period (Dose-optimization period and Dose maintenance period) multiplied by the number of capsules to be taken per day during the treatment period. If the number of capsules taken or returned is missing, then the compliance will be missing.

Descriptive statistics (counts and percentages) for investigational product compliance will be presented by treatment group of the antecedent studies and directly enrolled for each period between 2 consecutive visits as well as for the entire study for the Safety Analysis Set. The investigational product treatment compliance will be categorized as <80%, 80-120%, or >120%. The categorical data will be presented for the Safety Analysis Set.

Treatment compliance data will also be listed for all subjects in the Safety Analysis Set.

8.3 Investigational Product Accountability

The total number of capsules dispensed, returned and the difference (dispensed minus returned) will be summarized by treatment group of the antecedent study, directly enrolled and overall for the Safety Analysis Set. This information will also be listed for all subjects in the Safety Analysis Set.

9. PRIOR AND CONCOMITANT MEDICATION

Version 2015MAR01 DDE (Enhanced) of the World Health Organization (WHO) drug dictionary will be used to classify prior and concomitant medications by therapeutic class.

Prior medication is defined as any medication with the start date prior to the date of the first dose of investigational product in the SPD489-348 study. Concomitant medication is defined as any medication with a start date prior to the date of the first dose of investigational product in the SPD489-348 study and continuing after the first dose of investigational product in the SPD489-348 study or with a start date between the dates of the first and last doses of investigational product in the SPD489-348 study, inclusive. Any medication with a start date after the date of the last dose of investigational product in the SPD489-348 study will not be considered a concomitant medication. Any such medications will be listed only and flagged as a post-treatment medication.

Both prior and concomitant medication usage (including ADHD medication) will be summarized by the number and proportion of subjects in each treatment group of the antecedent studies and directly enrolled subjects, receiving each medication within each preferred term for the Safety Analysis Set. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once. Both prior and concomitant ADHD medication usage (based on indication), excluding investigational product, will also be summarized by the number and proportion of subjects in each treatment group of the antecedent studies receiving each medication within each preferred term for the Safety Analysis Set.

All medication will be listed for the Safety Analysis Set. Separate listings will also be provided for ADHD medication and ADHD Behavioral Therapy.

10. EFFICACY ANALYSES

All efficacy analyses will be based on the FAS. Efficacy data will be summarized by treatment group of the antecedent studies, directly enrolled subjects and overall. Baseline for all efficacy analyses is defined as the baseline value from the antecedent study, and for subjects that directly enrolled into SPD489-348, baseline is defined as the last observation prior to the first dose of investigational product in SPD489-348 study. There is no primary efficacy endpoint defined for this study. An efficacy measurement that is assessed more than 3 days after the date of the last dose of the investigational product will not be included for analysis.

All confidence intervals will be 2-sided 95% confidence intervals.

10.1 Efficacy Endpoints and Analysis

10.1.1 ADHD-RS-IV Preschool Version

The ADHD-RS-IV Preschool Version is an 18-item questionnaire that requires the respondent to rate the frequency of occurrence of ADHD symptoms as defined by Diagnostic and Statistical Manual of Mental Disorders Fourth Edition – Text Revision (DSM-IV-TR) criteria. Each item is scored on a 4-point scale ranging from 0 (never or rarely) to 3 (very often) with total score ranging from 0-54. The 18 items may be grouped into 2 subscales: hyperactivity/impulsivity (even numbered items 2-18) and inattentiveness (odd-numbered items 1-17).

A missing individual item in the ADHD-RS-IV Preschool Version will be imputed as follows:

- If only 1 single item is missing in a given subscale, the mean score for all other items in the subscale for the specific visit will be imputed as the score rounded up to the nearest integer for the missing score. The total score is computed as the sum of the imputed subscale scores.
- If more than 1 item is missing in a subscale then the subscale score will be set to missing.
- Both subscales must be non-missing in order to calculate the total score.

The efficacy endpoint for the ADHD-RS-IV Preschool Version is defined as the change from baseline on the clinician-administered ADHD-RS-IV Preschool Version total score.

The observed and change from baseline ADHD-RS-IV Preschool Version Total score will be summarized at each applicable visit using descriptive statistics (n, mean, SD, minimum, median, and maximum). The 95% confidence interval of the mean of the change from baseline value will also be presented for informational purposes.

The observed and change from baseline ADHD-RS-IV Preschool Version Hyperactivity/Impulsivity and Inattentiveness subscales will also be summarized.

Additionally, a corresponding line graph of the mean of the change from baseline value and associated 95% CI in ADHD-RS-IV Preschool Version Total Score by antecedent treatment group, directly enrolled and overall, and visit will be presented. A similar plot for Hyperactivity/Impulsivity and Inattentiveness subscales will also be presented.

All ADHD-RS-IV assessments will be listed.

10.1.2 Clinical Global Impression

The efficacy endpoint for the CGI-I will be analyzed by a method similar to that used for the ADHD-RS-IV total scores. In addition, CGI-I will also be analyzed using the proportion of subjects who had an "improved" CGI-I measurement. The CGI-I categories of "very much improved" and "much improved" will be classified as "improved" and all other assessed categories will be grouped together as "not improved".

The observed dichotomized CGI-I values will be summarized at each applicable visit using number of subjects and percentages. A corresponding bar chart showing the percentage of subjects improved by visit, antecedent treatment group, directly enrolled and overall will be presented, with 95% Clopper-Pearson (Exact) confidence interval.

Descriptive summary statistics will be presented by treatment group of the antecedent studies, directly enrolled and overall, for the CGI-I scores at each applicable visit.

The CGI data will be listed for the FAS.

11. SAFETY ANALYSES

The safety analysis will be performed using the Safety Analysis Set. Safety data will be summarized by treatment group of the antecedent studies, directly enrolled subjects and overall except for adverse events (AEs), which will be summarized by the last dose received prior to the AE start date. Safety variables include AEs, clinical laboratory variables, vital signs, physical examinations, Children's Sleep Habits Questionnaire (CSHQ), sleep diary, and ECG variables. Baseline for all safety variables is defined as the baseline value from the antecedent study or last observation prior to the first dose in SPD489-348 study for directly enrolled subjects.

11.1 Adverse Events

Adverse events (AEs) will be coded using Version 18.0 or newer of the Medical Dictionary for Regulatory Activities (MedDRA).

Only AEs recorded on the SPD489-348 eCRF will be included in summary tables and listings. AEs that are only recorded on the antecedent study eCRF will not be included.

An AE will be considered a treatment-emergent adverse event (TEAE) if it has a start date on or after the first dose of investigational product in this study, or if it has an AE start date before the date of the first dose of investigational product but increases in its severity on or after the date of the first dose of investigational product in this study. An AE that occurs more than 3 days after the date of the last dose of investigational product in the SPD489-348 study will not be counted as a TEAE.

An overall summary of the number of subjects with TEAEs will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to investigational product, TEAEs leading to withdrawal, severe TEAEs, and TEAEs leading to death.

The number and percentage of subjects reporting TEAEs in each onset dose level will be tabulated by system organ class (SOC) and preferred term. Further summaries will be produced for TEAEs by maximum severity and TEAEs related to investigational product. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

Serious TEAEs, TEAEs related to investigational product, TEAEs leading to discontinuation of investigational product and serious TEAEs leading to death will be summarized by SOC, preferred term and onset dose level.

All information about AEs collected on the eCRF will be listed alongside the dose, preferred term, and SOC. For Serious TEAEs, deaths, AEs related to the investigational product, and TEAEs leading to study discontinuation, a separate listing will also be provided.

11.2 Clinical Laboratory Variables

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for clinical laboratory values (in International System of Units (SI)) and changes from baseline at each assessment time point as well as shift tables from baseline to each visit for quantitative variables will be presented for the following clinical laboratory variables.

Biochemistry and Endocrinology

- Total cholesterol
- Aspartate transaminase (AST)
- Phosphorus
- Alanine transaminase (ALT)
- Sodium
- Alkaline phosphatase
- Potassium
- Gamma glutamyl transferase (GGT)
- Thyroid stimulating hormone (TSH)
- Free thyroxine (T4)
- Calcium
- Uric acid
- Blood urea nitrogen
- Total bilirubin
- Creatinine
- Glucose
- Albumin
- Total protein
- Lactate dehydrogenase

Hematology

- Hemoglobin
- Hematocrit
- Red blood cells (RBC)
- Platelet count
- White blood cell (WBC) count – total and differential
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Bands
- Mean corpuscular volume (MCV)

Urinalysis

- Glucose
- Specific gravity
- Blood
- Ketones
- Protein
- Bilirubin
- pH
- Urobilinogen
- Color
- Leukocyte esterase
- Nitrate

If urinalysis detects protein and/or blood, a microscopic examination will be conducted. The microscopic examination will consist of RBC, WBC, casts, and bacteria. These variables will be listed but not summarized.

Qualitative urinalysis variables will be summarized by the number of subjects in each category and the percentage of subjects out of the total in the safety analysis set with a valid result at the given visit.

All clinical laboratory values will be listed for the Safety Analysis Set.

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 4. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment group of the antecedent studies, directly enrolled and overall. The percentages will be calculated relative to the number of subjects with at least 1 available post-baseline assessment per parameter. The numerator is the total number of subjects with at least 1 post-baseline PCI value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline values.

Table 4 Criteria for Potentially Clinically Important Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Biochemistry			
Albumin	g/dL	< 3g/dL	-
Aspartate transaminase (AST)	-	-	≥ 3 x ULN
Alanine transaminase (ALT)	-	-	≥ 3 x ULN
Blood urea nitrogen	mg/dl	-	> 30mg/dl or > 2.5 x ULN
Calcium	mg/dL	< 8mg/dL	> 11.5mg/dL
Total cholesterol	mg/dL	-	> 300mg/dl
Creatinine	mg/dl	-	> 2mg/dl or > 1.5 x ULN
Gamma glutamyl transferase (GGT)	-	-	≥ 2.5 x ULN
Glucose	mg/dL	< 55mg/dL	> 160mg/dL
Lactate dehydrogenase	-	-	> 3 x ULN
Phosphorus	mg/dL	< 2.5mg/dL	> 7mg/dL
Potassium	mmol/l	< 3mmol/l	> 5.5mmol/l
Thyroid stimulating hormone (TSH)	-	< LLN	> 2 x ULN
Sodium	mEq/L	< 130mEq/L	> 150mEq/L
Uric acid	mg/dL	-	> 10mg/dL
Total bilirubin	mg/dL	-	> 2 mg/dL
Total protein	g/dL	< 5g/dL	> 9g/dL
Hematology			
Bands	-	-	> $0.27x10^3$/µL or > 5%

Table 4 Criteria for Potentially Clinically Important Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Basophils	-	-	> 10%
Hemoglobin	g/dL	< 9g/dl	> 16g/dl
Hematocrit	%	< 30%	> 50%
Platelet count	$10^3/\mu L$	$< 75x10^3/\mu L$	$> 600x10^3/\mu L$
Red blood cells (RBC)	$10^6/\mu L$	$< 2.5x10^6/\mu L$	-
White blood cell (WBC) count	$10^3/\mu L$	$< 3x10^3/\mu L$	$> 16x10^3/\mu L$
Neutrophils	-	$< 1x10^3/\mu L$ or < 30%	-
Eosinophils	%	-	> 10%
Lymphocytes	%	< 10%	> 70%
Monocytes	%	-	> 20%
Urinalysis			
Glucose	-	-	Positive Value (excluding trace)
Protein	-	-	Positive Value (excluding trace)
Blood	-	-	Positive Value (excluding trace)
Ketones	-	-	Positive Value (excluding trace)
Bilirubin	-	-	Positive Value (excluding trace)

LLN: Lower limit of normal value provided by the laboratory; ULN: Upper limit of normal value provided by the laboratory

11.3 Vital Signs

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for vital signs (systolic and diastolic blood pressure, pulse rate, body weight, temperature, and respiration rate) and their changes from baseline at each post-baseline visit will be presented by treatment group of the antecedent studies, directly enrolled subjects and overall.

Blood pressure and pulse measurements will be obtained 3 times with approximately 2 minutes in between each collection. The average of the three measurements collected at each nominal time point will be used for analysis. Blood pressure, pulse and respiratory rate will be determined after subject have remained seated for a minimum of 5 minutes.

Weight and BMI will also be converted to percentile values based on the subject's age at each visit and at the last on treatment assessment and summarized categorically. Descriptive statistics (n, mean, SD, minimum, median, and maximum) for weight and BMI percentile values and their changes from baseline at each post-baseline visit will also be presented by treatment group of the antecedent studies and overall. Post-baseline shifts in weight percentile category ($<5^{th}$, 5^{th} to $<95^{th}$, and $\geq 95^{th}$) and BMI percentile category ($<5^{th}$, 5^{th} to $<85^{th}$, 85^{th} to $<95^{th}$, and $\geq 95^{th}$) from baseline will be summarized at each visit as well as at the last on treatment assessment. In

addition, *z*-scores for weight and BMI will be based on the subject's age at each visit and will be summarized categorically by visit and at the last on treatment assessment. Percentiles and *z*-scores will be derived using the CDC growth charts (Kuczmarski et al., 2002).

Additionally, figures with the mean change from baseline ± SD of the vital signs values (systolic and diastolic blood pressure, and pulse), weight, and BMI will be presented by antecedent treatment group, directly enrolled, overall and visit. All vital sign values will be listed for the Safety Analysis Set.

Vital sign values will be considered PCI if they meet either the observed value criteria or the change from baseline criteria listed in Table 5. The number and percentage of subjects with PCI post-baseline values will be tabulated by treatment group of the antecedent studies, directly enrolled and overall, and for each visit. The percentages will be calculated relative to the number of subjects with at least 1 post-baseline assessment per parameter and visit by antecedent study treatment group, directly enrolled and overall. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline PCI values.

Table 5 Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Sitting Systolic blood pressure (mmHg)	High	≥120	Increase of >10
	Low	<75	Decrease of >10
Sitting Diastolic blood pressure (mmHg)	High	≥85	Increase of >10
	Low	<40	Decrease of >10
Pulse rate (beats per minute)	High	≥130	Increase of >15
	Low	≤55	Decrease of >15
Weight (kg)	High	-	Increase of ≥7%
	Low	-	Decrease of ≥7%
Temperature (deg. C)	High	>39	-
	Low	<35	-
BMI (kg/m^2)	High	>95th percentile for age and sex	-
	Low	<5th percentile for age and sex	-

[a] A post-baseline value is considered as a PCI value if it meets either the criteria for observed value or the criteria for change from baseline.

11.4 Electrocardiogram (ECG)

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for ECG variables (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point will be presented by treatment group of the

antecedent studies, directly enrolled subjects and overall. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/hr in the correction formula. ECG interpretation will be summarized by visit. A shift table from baseline to each visit for qualitative ECG results will also be presented.

All ECG values will be listed for the Safety Analysis Set.

Electrocardiogram variable values will be considered PCI if they meet either the observed value criteria or the change from baseline criteria listed in Table 6. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment group of the antecedent studies, directly enrolled and overall for each visit. The percentages for the observed value criteria will be calculated relative to the number of subjects with at least 1 post-baseline assessment available per parameter and visit. The percentages for the change from baseline criteria will be calculated relative to the number of subjects with available baseline and at least 1 post-baseline assessment per parameter and visit by antecedent study treatment group, directly enrolled and overall. The numerator is the total number of subjects with at least 1 PCI post-baseline ECG value. A listing of all subjects with post-baseline PCI value will be provided including the subject number, site, baseline, and post-baseline PCI values.

Table 6 Criteria for Potentially Clinically Important ECG Values

ECG Parameter	Unit	Observed Value		Change from Baseline	
		Lower Limit	Higher Limit	Lower Limit	Higher Limit
ECG Result	-	-	Abnormal (core lab) and Clinically significant from investigator	-	-
Heart Rate	beats/minute	<55	>130	Decrease >15	Increase >15
PR Interval	msec	-	≥200	-	-
QT Interval	msec	-	≥440	-	≥30 and <60 ≥60
QTcF Interval	msec	-	≥440 and <480 ≥480 and <500 ≥500	-	≥30 and <60 ≥60
QTcB Interval	msec	-	≥440 and <480 ≥480 and <500 ≥500	-	≥30 and <60 ≥60
QRS Interval	msec	-	≥90	-	-
Rhythm	-	-	Any rhythm other than sinus rhythm **ECG evaluation –abnormal rhythm** • Complete Heart Block • Tachycardia • Bradycardia • Wandering Atrial Pacemaker • Ectopic Atrial Rhythm • Atrial Fibrillation • Atrial Flutter • Multifocal Atrial Tachycardia • Supraventricular Tachycardia • Atrial Bigeminy • Ventricular Bigeminy • Atrial Couplets • Ventricular Couplets • Ventricular Tachycardia • Torsade des Pointes • Ventricular Fibrillation • Junctional Rhythm • Idioventricular Rhythm • Escape Beat • Atrial Pacemaker	-	-

11.5 Other Safety Variables

11.5.1 Children's Sleep Habits Questionnaire (CSHQ) and Sleep Diary

The CSHQ consists of 33 items for scoring and several extra items intended to provide administrators with other potentially useful information about respondents. The instrument evaluates the child's sleep based on behavior within 8 different subscales:

1. Bedtime resistance (sum of the responses for Goes to bed at same time, Falls asleep in own bed, Falls asleep in other's bed, Needs parent in room to sleep, Struggles at bedtime and Afraid of sleeping alone)
2. Sleep-onset delay (Falls asleep in 20 minutes),
3. Sleep duration (sum of the responses for Sleeps too little, Sleeps the right amount and Sleeps same amount each day),
4. Sleep anxiety (sum of the responses for Needs parent in room to sleep, Afraid of sleeping in the dark, Afraid of sleeping alone and Trouble sleeping away),
5. Night wakings (sum of the responses for Moves to other's bed in night, Awakes once during night and Awakes more than once),
6. Parasomnias (sum of the responses for Wets the bed at night, Talks during sleep, Restless and moves a lot, Sleepwalks, Grinds teeth during sleep, Awakens screaming, sweating and Alarmed by scary dream),
7. Sleep-disordered breathing (sum of the responses for Snores loudly, Stops breathing and Snorts and gasps),
8. Daytime sleepiness (sum of the responses for Wakes by himself, Wakes up in negative mood, Others wake child, Hard time getting out of bed, Takes long time to be alert, Seems tired, Watching TV and Riding in car).

The total score is the sum of the 33 individual items.

The total score, each subscale and each individual item will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) at each visit (and Visit 18/ET). All Children's Sleep Habits Questionnaire data will be listed for the Safety Analysis Set.

Sleep diary data will be summarized at each visit (and Visit 18/ET) for total daytime napping time, nighttime sleep time and time to fall asleep using descriptive statistics (n, mean, SD, minimum, median, and maximum). Sleep diary data is collected daily. The average daily value per visit and their change from baseline will be summarized. Sleep diary data will also be listed for the Safety Analysis Set.

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

The Pediatric/Cognitively Impaired Version of the scale will be used in the study. There are two versions of the C-SSRS.

If the subject participated in the antecedent study:

- The "Since Last Visit" version will be completed for all subjects at each visit in the study.

If the subject is directly enrolled in this study and did not participate in an antecedent study:

- The "Lifetime recent" version will be administered at the Screening Visit (Visit -1).
- The "Since Last Visit" version will be completed for all study visits after the Screening Visit (Visit -1).

Number of subjects and frequency with suicide-related events, based on the C-SSRS data, will be tabulated for the Safety Analysis Set for the following categories:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent
6. Preparatory acts or behavior
7. Aborted suicide, attempt
8. Interrupted attempt
9. Actual attempt (non-fatal)
10. Completed suicide
11. Self-Injurious behavior without suicidal intent

A listing of the C-SSRS data will be provided for subjects with a positive response for the Safety Analysis Set.

11.5.3 Follow-up Phone Call

A listing will be created to show the date of the follow-up phone call.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

13. OTHER ANALYSES

No other analyses are planned for this study.

14. INTERIM ANALYSIS

A Data Monitoring Committee (DMC) was set up to review the data pertaining to safety, tolerability, and benefit/harm of the study therapy for the duration of the Pediatric Written Request program. No interim statistical inference for any efficacy variable will be performed. For further details of the DMC, see Section 15.

15. DATA MONITORING/REVIEW COMMITTEE

An external independent DMC is involved in the management of this study. The purpose of the DMC, for this study, is to monitor safety and tolerability of the investigational product and to protect the interests of subjects in the study and of those still to be entered. Data will be provided to the DMC by a non-sponsor independent statistical and reporting group that is not assigned to the study.

Data used for DMC reporting purposes will have, at a minimum, the coding done for adverse events. Otherwise, while data may not be cleaned specifically for the DMC, routine cleaning will be done throughout the course of the study by subsets of subjects, as they complete / early terminate from the study.

Further details regarding the DMC can be found in the DMC charter.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no changes to the analyses specified in the protocol.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, SD, minimum, maximum. The minimum and maximum values will be presented to the same number of decimal places as the raw data. The mean and median will be presented to one more decimal place than the raw data. The SD will be presented to two more decimal places than the raw data. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be reported to 1 decimal place, except when the percentage equals exactly 100 where it will be displayed as an integer (100). For zero, only count and no percentage will be displayed. Post-baseline is defined as any visit which occurs after the first dose of investigational product in this study.

18.2 Treatment Group

For all tables summarized by the treatment group in the antecedent study, the actual treatment received will be used (SPD489 or Placebo) rather than the planned treatment.

18.3 Visit Mapping

The visits need to be mapped in the analysis datasets so that the visit numbers are aligned by the relative week as shown in Table 7 and Table 8.

Table 7 Visit Mapping for "A" Subjects

Protocol Visit Name	Protocol Visit Number	Mapped Visit Name	Mapped Visit Number
Not applicable (from antecedent study)	Not applicable	Baseline	0
Visit 0 (Baseline)[a]	0	Week 0	3
Visit 1 (Week 4)	4	Week 4	7
Visit 2 (Week 8)	7	Week 8	10
Visit 3 (Week 12)	8	Week 12	11
Visit 4 (Week 16)	9	Week 16	12
Visit 5 (Week 20)	10	Week 20	13
Visit 6 (Week 24)	11	Week 24	14
Visit 7 (Week 28)	12	Week 28	15
Visit 8 (Week 32)	13	Week 32	16
Visit 9 (Week 36)	14	Week 36	17
Visit 10 (Week 40)	15	Week 40	18
Visit 11 (Week 44)	16	Week 44	19
Visit 12 (Week 48)	17	Week 48	20
Visit 13/ET (Week 52)	18	Week 52/ET	21
Safety Follow-up (Week 53)	-	Week 53	22

[a] Visit 0 is the same day as the End of Study Visit for the antecedent study

Table 8 Visit Mapping for Subjects for "B" Subjects and those under Protocol Amendent 2, 20 Oct 2017

Protocol Visit Name	Protocol Visit Number	Mapped Visit Name	Mapped Visit Number
Not applicable (from antecedent study)	Not applicable	Baseline	0
Visit -1 (Screening)[a]	-1	Week -4 to -1	1
Phone Call	-	Week -1 to 0	2
Visit 0 (Baseline)	0	Week 0	3
Visit 1 (Week 1)	1	Week 1	4
Visit 2 (Week 2)	2	Week 2	5
Visit 3 (Week 3)	3	Week 3	6
Visit 4 (Week 4)	4	Week 4	7
Visit 5 (Week 5)	5	Week 5	8
Visit 6 (Week 6)	6	Week 6	9
Visit 7 (Week 8)	7	Week 8	10
Visit 8 (Week 12)	8	Week 12	11
Visit 9 (Week 16)	9	Week 16	12
Visit 10 (Week 20)	10	Week 20	13
Visit 11 (Week 24)	11	Week 24	14
Visit 12 (Week 28)	12	Week 28	15
Visit 13 (Week 32)	13	Week 32	16
Visit 14 (Week 36)	14	Week 36	17
Visit 15 (Week 40)	15	Week 40	18
Visit 16 (Week 44)	16	Week 44	19
Visit 17 (Week 48)	17	Week 48	20
Visit 18/ET (Week 52)	18	Week 52/ET	21
Safety Follow-up (Week 53)	-	Week 53	22

[a] For roll-over subjects, the Screening (visit -1) is the same day as the End of Study Visit for the antecedent SPD489-347 Study.

18.4 Derived Efficacy Endpoints

Not applicable.

18.5 Repeated or Unscheduled Assessments of Safety Parameters

If end of study assessments are repeated or unscheduled, the last post-baseline assessment whilst on investigational product will be used. However, all post-baseline assessments will be used for PCI value determination and all assessments will be presented in the data listings.

18.6 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Analysis Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration. If date of last visit when product was returned is missing, then use the date of discontinuation in the calculation of treatment duration, otherwise use date of cut-off.

18.7 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first. The first and last dose of investigational product refers to the SPD489-348 study.

18.7.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same, but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day

- If either the year is after the year of the date of the first dose of investigational product or if both years are the same, but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

18.7.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same, but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same, but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

18.8 Missing Date Information for Adverse Events

For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first. The first dose of investigational

product refers to the SPD489-348 study. For all subjects, the last dose of investigational product refers to the SPD489-348 study.

18.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same, but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

18.8.2 Incomplete Stop Date

No imputation will be performed on incomplete stop dates.

18.9 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be

assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.10 Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

18.11 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable. The appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

Table 9 Examples for Coding of Special Character Values for Clinical Laboratory Variables

Clinical Laboratory Test	Possible Results (in SI units)	Coded Value for Analysis
Chemistry: ALT	<5	0
Chemistry: AST	<5	0
Chemistry: Total Bilirubin	<2	0
Urinalysis: Glucose	≥55	Positive
	≤0	Negative
Urinalysis: pH	≥8.0	8.0

19. REFERENCES

Kuczmarski, R. J., Ogden, C. L., Guo, S. S., Grummer-Strawn, L. M., Flegal, K. M., Mei, Z., Wei, R., Curtin, L. R., Roche, A. F.and Johnson, C. L. 2002. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11*, 1-190.

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16.2.7.5	Adverse Events with Fatal Outcome (Safety Analysis Set)	Y
16.2.8.1	Clinical Laboratory Test Results (Safety Analysis Set)	Y
16.2.8.2	Subjects with Potentially Clinically Important Laboratory Test Results (Safety Analysis Set)	Y
16.2.8.3	Vital Signs (Safety Analysis Set)	Y
16.2.8.4	Subjects with Potentially Clinically Important Vital Signs (Safety Analysis Set)	Y
16.2.8.5	12-Lead ECG Results and Interpretation (Safety Analysis Set)	Y
16.2.8.6	Subjects with Potentially Clinically Important ECG Results (Safety Analysis Set)	Y
16.2.8.7	Children's Sleep Habits Questionnaire (CSHQ) (Safety Analysis Set)	N
16.2.8.8	Sleep Diary (Safety Analysis Set)	N
16.2.8.9	Columbia-Suicide Severity Rating Scale: Suicidal Ideation (Safety Analysis Set)	Y
16.2.8.10	Columbia-Suicide Severity Rating Scale: Intensity of Ideation (Safety Analysis Set)	Y
16.2.8.11	Columbia-Suicide Severity Rating Scale: Suicidal Behavior (Safety Analysis Set)	Y
16.2.8.12	Columbia-Suicide Severity Rating Scale: Suicidal Behavior - Actual Attempts (Safety Analysis Set)	Y
16.2.8.13	Follow-Up Call (Safety Analysis Set)	N